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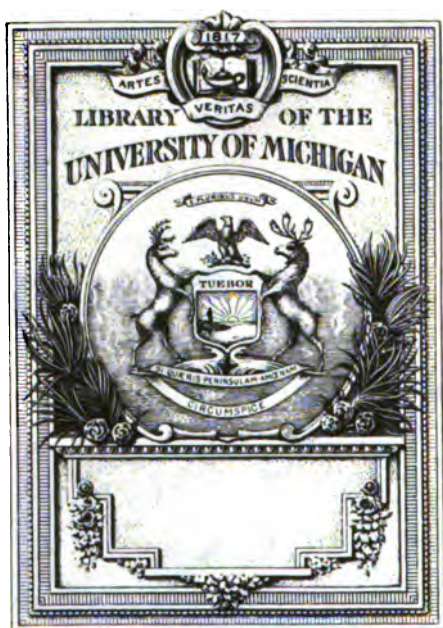
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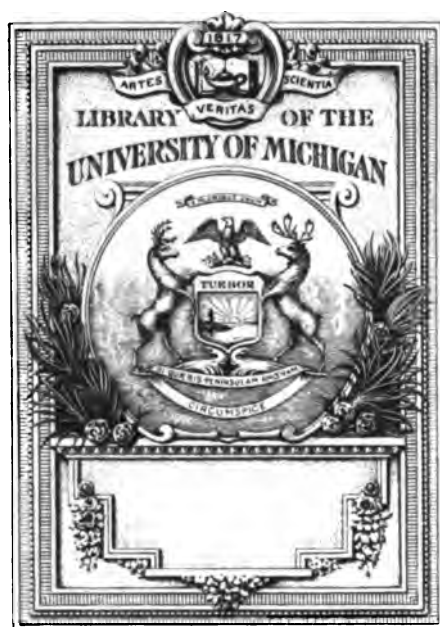
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ORGANIC CHEMISTRY

FOR

ADVANCED STUDENTS

BY
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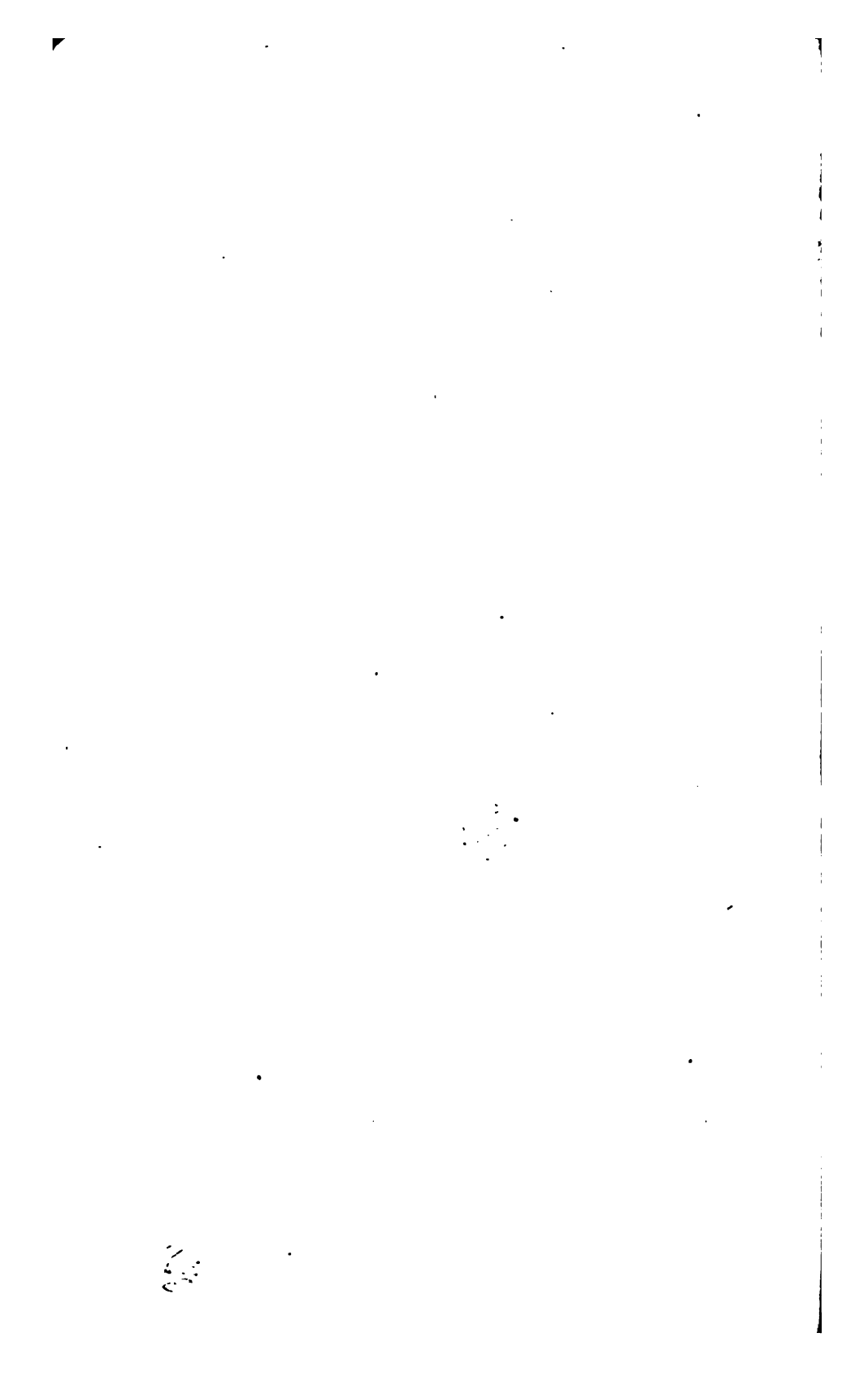
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PREFACE

THESE essays have been prepared from notes of lectures delivered to senior students, and are intended only for those who have completed an elementary course of organic chemistry.

Their publication is the result of an annually recurring demand from my class for a suitable book having reference to the lectures, which the larger text-book of organic chemistry does not exactly meet, and it seemed to me that what was needed by my own students might be welcome elsewhere.

Although the usual text-book arrangement has obvious and unquestionable advantages for the beginner who requires to docket and pigeon-hole his facts on some simple system, these advantages are lost on the advanced student in the same sense that the interest of a story for one who had learnt to read would be destroyed by rearranging all the words as different parts of speech.

No essential difference is, as a rule, to be found between the elementary and advanced text-book except that of quantity, yet when a knowledge of the principles of classification and of the properties of fundamental groups has been acquired, the mere enumeration and description of more compounds cannot be regarded as marking a real advance. In my own senior class I have attempted to present the subject somewhat in the manner in which it has naturally developed. I have selected a series of chapters dealing with different topics, and have elaborated these topics as far as possible in conformity with their actual history—in other words, I have subordinated systematic classification to the development of general principles and to the study of structure.

The success of the series of monographs on chemical subjects which, under the title of *Ahrens' Vorträge*, have appeared in Germany, where there is no dearth of first-rate text-books,

encourages my belief in the value of this mode of treatment. It simply means that as science grows it divides and subdivides, and these subdivisions become the objects of special study. As study becomes specialized in this way, so, I am convinced, will advanced teaching, and this conviction must justify the present departure from the traditional system of classification.

This book is not in any sense a book of reference. It covers a limited area of organic chemistry, and even this is incompletely surveyed. On the other hand, though the topics are restricted in number, they command collectively a fairly wide range of the more important divisions of the subject.

In conclusion, I have to acknowledge the generous assistance of my friend and former colleague Dr. H. D. Dakin, especially in connection with the chapters on *Fermentation*, *The Purine Group* and *The Proteins*, and also of Prof. A. Smithells and Dr. H. M. Dawson, who have helped me on many occasions with valuable suggestions.

J. B. COHEN.

THE UNIVERSITY OF LEEDS,
July, 1907.

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ORGANIC CHEMISTRY

CHAPTER I

HISTORICAL INTRODUCTION

The Radical¹ of Benzoic Acid. In the year 1832 Liebig and Wöhler published their classical memoir, entitled, 'Experiments on the Radical of Benzoic Acid'.²

Viewed in the light of our present knowledge there is nothing very remarkable in the facts which they discovered. Starting with bitter almond oil, which we now term *benzaldehyde*, they converted it by the action of chlorine and bromine into benzoyl chloride and bromide. Benzoyl chloride treated successively with potassium iodide gave benzoyl iodide; with ammonia, benzamide; with lead sulphide, benzoyl sulphide; with mercuric cyanide, benzoyl cyanide and with alcohol, benzoic ether. Bitter almond oil had, moreover, been found by Stange (1824) to undergo rapid oxidation in the air and to be transformed into an acid—benzoic acid—identical with the substance derived from gum benzoin.

Such is briefly the substance of the investigation to which the following introduction is attached. 'When a chemist is fortunate enough to perceive one ray of light penetrating the dark region of organic nature, which may mark the entrance to the right path of future knowledge, he has reason to feel encouraged, although conscious of the vastness of the field which lies before him.'

In order to realize the importance of a memoir which created a profound impression among contemporary chemists, and was welcomed by Berzelius as 'the dawn of a new day', we must take a glance at the branch of chemistry which at this period formed 'the dark region of organic nature'.

Origin of the Radical Theory. If we turn to Lemery's *Cours de Chymie*, which was the popular text-book from 1675 down to the middle of the eighteenth century, we find all known substances

¹ It is an interesting and curious fact that with admittedly 'little to recommend it' (*Trans. Chem. Soc.*, 1905, 87, 548) the Chemical Society of Great Britain has seen fit to alter the original spelling to 'radicle', and the Society now holds the unique position of being the only representative body of chemists which has adopted this spelling.

² Liebig's *Annalen*, 1832, 3, 249; Ostwald's *Klassiker*, No. 22.

distributed according to their origin between the mineral, vegetable and animal kingdoms. Under the two divisions of vegetables and animals occur the names of substances which have been known from remote times, such as sugar, starch, fats and oils, gums and resins. By the process of distillation alcohol had been obtained from fermented liquids, acetic acid from vinegar, turpentine from resin, and various sweet scented oils from plants. Vegetable colouring matters were employed in dyeing, and oils and fats in the production of soap. Extracts of cinchona bark, opium and other vegetable substances were used in medicine. Towards the close of the eighteenth century Scheele isolated and clearly distinguished the acid principles present in various vegetable and animal products. He found malic acid in apples, citric acid in lemons, oxalic acid in wood sorrel, gallic acid in galls, lactic acid in sour milk, and uric acid in urine. He also obtained from olive oil, by boiling it with lead oxide, a sweet, viscid liquid, which we now know as glycerine.

These varied products of animal and plant life which, when ignited took fire, or when heated in closed vessels charred and gave off water and other volatile matters, contained, according to the views of the phlogistonists, more of the aqueous and combustible principle or phlogiston, than mineral substances. They were termed *organic* to indicate their origin from living or organized matter.

With Lavoisier's discovery of the cause of oxidation and combustion, the element oxygen became in chemistry very much what the sun is in our solar system. The chemistry of Lavoisier was the chemistry of oxygen. All compounds were oxides, generally simple oxides of another element. To the other element attached to oxygen de Morveau applied the term *base* or *radical*. The simple oxides were divided into salifiable and acidifiable bases, and these united to form salts.¹ The system was essentially dualistic, and contained the germ of the theory subsequently developed by Berzelius. Lavoisier, who was the first to demonstrate the true composition of organic substances, extended the idea of radical so as to embrace these compounds (1784). Organic substances which generally contained carbon, hydrogen, and oxygen, and occasionally nitrogen and phosphorus, were regarded as oxides of a radical, composed of at least two elements, carbon and hydrogen. Sugar, which yielded oxalic acid on oxidation, was the oxide of a hydrocarbon radical, and oxalic acid formed its higher oxide. *The radical was purely hypothetical.* Indeed, so little was then known about the nature of organic compounds *that*, with the advent of the atomic theory,

¹ Lavoisier's *Elements of Chemistry*, translated by Kerr, 1802, I, 289.

it was held to be doubtful if the elements composing them combined in simple atomic proportion and obeyed the laws of combination which had been found to obtain in the province of inorganic chemistry. Organic compounds were the products of a *vital force*, not necessarily dependent on the chemical laws governing inert matter. This view was commonly held until Berzelius, in 1814, by improving the method of organic analysis, showed from the results of his analyses of sugar and some of the organic acids, that organic compounds were subject to the ordinary laws of chemical combination.

Berzelius adopted Lavoisier's view of the nature of organic compounds; for in his *Treatise on Chemistry* (2nd edition), published in 1817, he says: 'After having become more closely acquainted with the difference between the products of organic and inorganic Nature and the different manner in which their constituents are combined together, we have found the difference to consist in this: that in inorganic Nature all oxidized bodies possess a *simple radical*, whilst all organic substances consist of oxides of *compound radicals*. In vegetable substances the radical consists usually of carbon and hydrogen, and in animal products of carbon, hydrogen, and nitrogen.'

To follow the history of organic chemistry from this point, and to realize the network of difficulties in which its votaries became gradually and unconsciously entangled, it will be necessary to understand the electro-chemical system of Berzelius and the method of notation which was founded upon it.

The Atomic and Molecular Weights of Berzelius. The discovery, in 1808, of Gay Lussac's law governing gaseous combination or the 'law of volumes', as it was commonly called, of Dulong and Petit's law (1819) which determined the relation of specific heats to the combining weights of the elements, and of Mitscherlich's law of isomorphism (1820) enabled Berzelius, after a careful revision of the combining proportions of the elements, to assign atomic weights based upon principles which we still recognize and adopt. Thus, if equal volumes of elementary gases contain the same number of atoms, the formula for water must be represented by H_2O since two volumes of hydrogen unite with one volume of oxygen; NH_3 will stand for ammonia, and HCl for hydrochloric acid. The method did not involve any question as to the volumes occupied by the combined gas, which offered a difficulty only solved later when Avogadro's distinction of *molécules constituantes*, and *intégrantes*, or, as we now say, atoms and molecules, was clearly recognized.¹ The

¹ *Die Grundlagen der Molekulartheorie*, Ostwald's *Klassiker*, No. 8; Avogadro and Dalton, by A. N. Meldrum, pub. W. F. Clay, Edin.

direct application of the law of volumes was limited to comparatively few elements. A wider range of atomic weights was derived from the specific heats of the metals and the isomorphism of their salts. Where none of these principles could be applied the atomic weights were ascertained by the simplest gravimetric relation of an element to oxygen in its oxide. The atomic weights of the metals which formed basic oxides were derived from these oxides which were assumed to contain a single atom of each element. Consequently the atomic weights of the alkali metals and of silver which formed isomorphous salts with them, received double their present values. The formulae for potassium and silver oxide and chloride were written KO , KCl_2 , AgO , AgCl_2 ; the formulae of ammonia and hydrochloric acid, originally written NH_3 and HCl , were afterwards doubled by using the *barred* or double atom thus: $\text{NH}_3 = \text{N}_2\text{H}_6$ and $\text{HCl} = \text{H}_2\text{Cl}_2$ with the object of making them equivalent to the atomic weights of the metals. For the same reason H_2 was the equivalent of 1 atom of oxygen and the formula for water appeared as $\text{HO} = \text{H}_2\text{O}$.

The series of atomic weights elaborated by Berzelius with rare analytical skill and an unerring instinct, which guided him where principles failed, differ little from the modern values.

In the third column of the following table is a list of the more important atomic weights taken from Berzelius' revised numbers, which appeared in 1826, oxygen being 100. The fourth column contains the figures calculated with hydrogen as the unit; in the fifth column are the present values:

Name.	Formula.	Berzelius' numbers.		Present numbers. H = 1
		O = 100	H = 1	
Oxygen	O	100	16.026	15.88
Hydrogen	H	6.289	1.000	1.00
Nitrogen	N	88.518	14.186	18.98
Sulphur	S	201.165	32.289	31.83
Phosphorus	P	196.155	31.486	30.77
Chlorine	Cl	221.325	35.470	35.18
Iodine	I	768.781	126.206	126.90
Fluorine	F	116.900	18.784	18.90
Carbon	C	76.437	12.250	11.91
Potassium	K	489.916	78.515	39.86
Sodium	Na	290.897	46.620	22.88
Silver	Ag	1851.607	216.611	107.12
Calcium	Ca	256.019	41.080	39.80
Strontium	Sr	547.285	87.709	86.94
Barium	Ba	856.880	137.325	136.40
Iron	Fe	339.213	54.868	55.50
Aluminium	Al	171.167	27.431	26.90
Chromium	Cr	351.819	56.883	51.70

ATOMIC AND MOLECULAR WEIGHTS OF BERZELIUS 5

In a memoir published in 1826, 'Sur quelques points de la théorie atomistique,' Dumas¹ attempted to extend the application of Avogadro's hypothesis to the determination of both atomic and molecular weights from the densities of gases and vapours, in connection with which he devised his well-known method. It is a curious fact that he not only failed to commend his method to the chemical world, but ended by convincing himself of its futility.

The result was due partly to a clumsy way of presenting his ideas, and partly to the confusion introduced by the anomalous vapour densities of some of the elements. Dumas set forth that equal volumes contain the same number of atoms or molecules; consequently, if one volume or atom of hydrogen unites with one volume or atom of chlorine to form two volumes or atoms of hydrochloric acid, the original atoms of hydrogen and chlorine are divisible into half atoms of each element. A half atom of oxygen must for the same reason be present in the atom of water and so forth. Though Dumas, no doubt, clearly distinguished between his physical atoms or molecules and his chemical or half atoms, the subdivision of the atom implied a contradiction in the term and did not fail to call forth criticism. As Dalton said, 'No man can split an atom.'²

But this was not all. Dumas' atomic weight for silicon, which he correctly interpreted from the vapour density of the chloride, differed from the number obtained by Berzelius, who derived it from the oxide, written SiO_3 from its analogy with SO_3 , CrO_3 , &c. The atomic weight of mercury, determined from the vapour density of the metal, was half that assigned by Berzelius from its specific heat. Finally, the anomalous vapour densities of phosphorus, sulphur, and, as Mitscherlich found later, arsenic, gave atomic weights which conflicted with those previously derived by Dumas himself from the vapour densities of their hydrides and chlorides and shook his confidence in his own method.

Berzelius' system of atomic weights also had its critics. As we have seen, doubt had been thrown by Dumas on the validity of the law of volumes. The atomic weights of several of the elements which were derived from the specific heats did not conform to the atomic weights deduced from the law of isomorphism; for example, the isomorphism of the silver salts and those of the alkalis fixed the atom of silver at 216, whilst its specific heat gave the number 108. Mitscherlich's law itself was not free from objection, inasmuch

¹ *Ann. Chim. Phys.*, 1826, 33, 387.

² *Memoirs of Dalton*, by Dr. Henry.

as the existence of dimorphous substances left the choice in some cases doubtful.

The principles which served Berzelius for his determinations gradually fell into discredit.

Gmelin's Equivalents. Leopold Gmelin, the author of the classical treatise which bears his name, suggested a reversion to the system of *equivalents*, a term introduced by Wollaston in 1808. It represented the simplest gravimetric relations, without reference to the law of volumes, and received strong support from Faraday's newly discovered electrolytic law (1832).

The old and new systems were easily reconciled by using the barred or double atom of Berzelius, and appeared side by side for many years without giving rise to confusion, until the double atom eventually disappeared. Kolbe was one of the last to use the barred atom of Berzelius, which he abandoned about 1850 in favour of the equivalent notation.

The following formulae for water, hydrochloric acid, ammonia, and phosphoric oxide, represent the original and modified notation of Berzelius and the corresponding equivalent notation of Gmelin :

Berzelius	{ original formula	H ₂ O	H ₂ Cl ₂	N ₂ H ₆	P ₂ O ₅
(H = 1; O = 16)	{ modified „	HO	HCl	NH ₃	PO ₅
Gmelin	equivalent „	HO	HCl	NH ₃	PO ₅
(H = 1; O = 8)					

Henceforth, densities of volatile organic compounds, though frequently determined with the object of controlling analytical results, never served as a means of ascertaining molecular weights until many years had elapsed, when Gerhardt and Laurent revived the hypothesis of Avogadro and Ampère. The aggregate weight of the atoms might correspond to one, two, or a multiple of two volumes of the vapour compared with one volume of hydrogen.

The formulae for chloral C₄Cl₆H₂O₂, chloroform C₂H₂Cl₆, alcohol C₄H₁₂O₂, and acetic ether C₆H₁₆O₄, corresponded to four volumes, whereas those for ether C₄H₁₀O, oxalic ether C₆H₁₀O₄, and succinic ether C₆H₁₄O₄, corresponded to only two volumes. It was left to the choice of the investigator to select an appropriate molecular formula. We shall presently see how the confusion, which arose from the absence of any recognized method for fixing molecular weights, resulted in many a fruitless and embittered controversy.

Berzelius' Electro-chemical Theory. The electro-chemical theory of Berzelius (1819) dominated chemistry during the first third of the

last century. Carefully elaborated in the case of inorganic compounds, it was sought to apply it in the same comprehensive manner to organic compounds. It was the guiding principle to which Berzelius clung throughout his life. But the young and rapidly growing branch of the science was not to be crippled by an artificial system which arrested its natural development. After a fierce controversy between Berzelius and the chemists of the French school the theory was finally abandoned. The theory may be briefly defined as Lavoisier's dualistic views expressed in the light of Davy's and Berzelius' electro-chemical researches. Each atom of the elements was supposed to possess opposite electrical poles provided with different quantities of electricity, so that it contained a surplus of one or other kind of electricity, and was either positive or negative according to the predominating polarity. It was by virtue of their opposite polarities that the atoms combined. The simple combinations of positive and negative elements furnished compounds of the *first order*. The electricities in these compounds were not necessarily neutralized, and there might still remain a surplus positive or negative charge which enabled them to enter into further combinations, forming compounds of the *second order*. The elements were arranged in electrical series with oxygen at one end, representing the most electro-negative element, and the alkali metals at the other, representing the most electro-positive elements. Each intermediate element would be electro-positive to the one that preceded and electro-negative to that which followed. The metals were strongly, the non-metals weakly electro-positive towards oxygen. The lower metallic oxides retained, therefore, a residual positive, the non-metallic oxides a residual negative polarity. Thus potash KO was electro-positive, whilst sulphuric acid SO_3 was electro-negative. Potash and sulphuric acid could therefore combine, by virtue of their opposite polarities, to form sulphate of potash, which was written $\text{SO}_3 + \text{KO}$. The electricities might still remain unneutralized, and by the formation of double salts such as potash alum, compounds of the *third order* were obtained.

The oxides of the non-metals were called acids; N_2O_5 stood for nitric acid and $\text{N}_2\text{O}_5 + \text{H}_2\text{O}$ was its hydrate. When the combined water of the hydrate or *basic water* was replaced by a metallic oxide or base, a neutral salt resulted. The same principle was applied to organic acids and their salts. Acetic acid was written $\text{C}_4\text{H}_6\text{O}_3$ and its hydrate (our acid) $\text{C}_4\text{H}_6\text{O}_3 + \text{H}_2\text{O}$; C_2O_3 stood for oxalic acid, and the crystalline compound which we now term anhydrous oxalic acid $\text{C}_2\text{O}_3 + \text{H}_2\text{O}$ was regarded as its hydrate; benzoic acid was $\text{C}_{14}\text{H}_{10}\text{O}_3$ and

its hydrate (our acid) was $C_{14}H_{10}O_3 + H_2O$. The molecular formula for the acids was derived from the composition of the salts, usually the silver salts, and as all salts were supposed to contain one atom of base (silver and the alkalis had double their present atomic weights), it necessarily followed that all monobasic acids, like acetic and benzoic, had double their present formulae, whereas dibasic acids received their modern values. It should be observed that these so-called organic acids only existed in the form of their hydrates, the acids themselves being purely fictitious groups of elements.

Organic Chemistry in 1830. In 1830 Liebig introduced his new method of organic analysis, which is essentially the one we still employ.¹ There is no doubt that the simplicity and rapidity of this process gave a new impulse to the study of organic chemistry. To perform an organic analysis appears to have been a troublesome business, for in a letter from Wöhler to Liebig written in August, 1830, we read: 'A thousand thanks for your quick reply. To be able to complete an analysis so rapidly is scarcely within the power of any one but yourself, certainly not in mine, for I have a wholesome dread of doing one.'

Organic chemistry in 1830 embraced a large number of substances of widely different properties, yet composed usually of only three or four elements—carbon, hydrogen, oxygen, and nitrogen. It included a variety of organic acids and a steadily increasing number of organic bases or alkaloids, the first of which—morphium—had been isolated in 1817 by Sertürner from opium; also a number of indifferent substances—hydrocarbons, spirits of wine, sugar, starch, gums—and finally, the fats and fixed oils, the composition of which had been studied by Chevreul in so complete and masterly a fashion that our knowledge of these substances has not materially advanced since his day. He showed that these bodies were compounds of glycerine with various acids (the fatty acids) and that they behaved like acetic ether, decomposing with alkalis into the salt of the acid and glycerine. There was, however, little analogy between the complexity of all these bodies and the simple compounds of inorganic chemistry, in which one element united with another in one or two, more rarely in three, proportions. Berzelius² at first distinguished inorganic compounds as binary, that is to say, divisible and sub-divisible into two parts, one electro-positive and the other electro-negative, whilst organic compounds contained more than two elements which were

¹ Berzelius, *Jahresb.*, 1831, 11, 214; Pogg., *Ann.*, 1831, 21, 1.

² *Ann. Phil.*, 4, 323.

directly combined into a whole and could not be subdivided or reunited after the manner of inorganic compounds. Hydrocarbons like marsh gas and turpentine, since they contained only two elements, were consequently classed among inorganic compounds, and occur under this head in the earlier numbers of Berzelius' *Jahresbericht*. But this distinction was not long maintained. Organic chemistry was still essentially the chemistry of animal and plant products and their derivatives. It is true that from time to time the artificial production of natural substances was announced. As far back as 1776 Scheele had obtained oxalic acid identical with that in wood sorrel by the oxidation of sugar with nitric acid. In 1822 Döbereiner had prepared formic acid, hitherto obtained by the distillation of ants, by the oxidation of tartaric acid, and had also converted alcohol into acetic acid by the aid of platinum black. In 1826 Hennel had synthesized alcohol from olefiant gas.¹ Again, in 1828, Wöhler found that in attempting to obtain ammonium cyanate by the action of ammonium chloride upon silver cyanate, or ammonia on lead cyanate, a crystalline compound was formed which was identified as urea, a substance only previously found in urine. But none of these artificially prepared substances was entirely independent of an animal or vegetable origin. Even the cyanates were derived in the first instance from potassium ferrocyanide, in the preparation of which animal matter was employed. These facts did little to disturb the belief in a vital force. Both Döbereiner's and Wöhler's discoveries are referred to by Berzelius in his *Jahresbericht*,² but it is clear that the rare example of isomerism furnished by the conversion of ammonium cyanate into urea created a far deeper impression than the realization of this much quoted synthesis (see p. 56).

Before the year 1832 the only organic substance from which a number of simple derivatives had been obtained was alcohol. With sulphuric acid it was known to yield, according to the conditions of the experiment, sulphovinic acid, ether, olefiant gas and a substance known as *oil of wine* of the formula $(CH_2)_n$; with hydrochloric acid it gave hydrochloric ether; with nitric acid, nitric (nitrous) ether; with acetic acid, acetic ether, and with oxalic acid, oxalic ether. Further, the oil of the Dutch chemists, as it was called, was obtained by combining olefiant gas with chlorine, and Hennel showed that sulphovinic acid was formed by the union of olefiant gas and sulphuric acid.³ The relationship of alcohol to its derivatives was a matter of general

¹ *Phil. Trans.*, 1826, 240; 1828, 365; *Pogg., Ann.*, 1827, 9, 21; 1828, 14, 282. See also *Chemical Synthesis of Vital Products*, p. 2, by R. Meldola, 1905.

² *Jahresb.*, 1828, 2, 160; 1829, 9, 266.

³ *Pogg., Ann.*, 1828, 14, 273; *Phil. Trans.*, 1826, Pt. 2, 240.

speculation which had free play, since no recognized method for ascertaining molecular weights existed.

The Etherin Theory. In 1828 Dumas and Boullay¹ propounded a theory which was intended to show the relationship of these substances. It was based upon an observation of Gay-Lussac's that the vapour density of ether was equivalent to that of one volume of olefiant gas and half a volume of water vapour, whereas that of alcohol was equivalent to half a volume of olefiant gas and half a volume of water vapour. Dumas and Boullay regarded alcohol, ether, and all their derivatives as containing one common group of elements, olefiant gas, which had the formula $2C_2H_2$, corresponding to the modern C_2H_4 (the atomic weight of carbon was derived by Dumas from the vapour density of marsh gas and olefiant gas, which he wrote CH_2 and C_2H_2 respectively, giving the number 6 to carbon). To the central group Berzelius gave the name of *etherin*, by which he signified oil of wine and denoted it by the formula² C_4H_8 , but the fundamental idea was the same in both, and the theory was henceforth known as the *etherin theory*.

In addition to presenting a series of related compounds as containing a common group or radical, it explained Hennel's preparation of sulphovinic acid from ethylene and sulphuric acid, the existence of oxamethane (oxamic ester) obtained by Dumas from oxalic ester and ammonia gas and the curious inflammable platinum organic compounds of Zeise, which the latter prepared by the action of alcohol on platinic chloride and which contained no oxygen.³

An essential part of Dumas and Boullay's theory was to institute a comparison between etherin and its derivatives and ammonia and its compounds, which were written as follows:

	Formulas of Dumas and Boullay.	Formulae of Berzelius.	Ammonia and its Compounds.
Olefiant gas	$2C_2H_2$	C_4H_8	N_2H_6
Hydrochloric ether	$2C_2H_2 + HCl$	$C_4H_8 + 2HCl$	$N_2H_6 + 2HCl$
Ether	$4C_2H_2 + H_2O$	$C_4H_8 + H_2O$	$N_2H_6 + H_2O$
Alcohol	$4C_2H_2 + 2H_2O$	$C_4H_8 + 2H_2O$	—
Acetic ether	$4C_2H_2 + C_2H_4O_3 + H_2O$	$C_4H_8 + C_2H_4O_3 + H_2O$	$N_2H_6 + C_2H_4O_3 + H_2O$
Nitric ether	$4C_2H_2 + N_2O_5 + H_2O$	$C_4H_8 + N_2O_5 + H_2O$	$N_2H_6 + N_2O_5 + H_2O$
Oxalic ether	$4C_2H_2 + C_2O_3 + H_2O$	$C_4H_8 + C_2O_3 + H_2O$	$N_2H_6 + C_2O_3 + H_2O$
Oxamethane	$4C_2H_2 + C_2O_3 + NH_3$	$C_4H_8 + C_2O_3 + NH_3$	—
Sulphovinic acid	$4C_2H_2 + 2SO_3 + 2H_2O$	$C_4H_8 + S_2O_6 + 2H_2O$	—
Zeise's compound	$4C_2H_2 + 2PtCl_2$	$C_4H_8 + Pt_2Cl_4$	—

¹ *Ann. Chim. Phys.*, 1828, (2), 36, 294; (2), 37, 15.

² *Jahresb.*, 1832, 12, 808.

³ *Annalen*, 1834, 9, 1.

Dumas and Boullay went so far as to state that olefiant gas, were it but soluble in water, would exhibit alkaline properties, and they even attempted to extend their theory so as to embrace compounds like the fats and oils, which were assumed to possess an imaginary hydrocarbon radical united to ether, and even the sugars which were described as carbonates of etherin. The theory found many supporters and long held its ground in France. Berzelius, on the other hand, gave it a half-hearted reception,¹ which soon changed to undisguised hostility. He pointed out that the existence of the radical C_4H_8 might be accepted as a mere matter of convenience, but that the formula for alcohol could be equally well represented by either $C_4H_8 + 2H_2O$ or $C_4H_{10}O + H_2O$. The fact of alcohol yielding olefiant gas was no more a reason for the presence of this group in alcohol than there was for the pre-existence of nitrous oxide in nitrate of ammonia merely because nitrous oxide was evolved on heating. If olefiant gas were alkaline, then surely alcohol and ether, which were soluble hydrates, should also have alkaline properties. Moreover, though olefiant gas could be prepared from alcohol, neither alcohol nor ether could be formed by the reverse process of adding water to olefiant gas, and the analogy with ammonia broke down.

Furnished with fresh weapons Berzelius returned to the attack in the following year.² Liebig and Wöhler had shown that sulphovinic acid had the formula $C_4H_8 + 2SO_3 + 2H_2O$, containing, therefore, two atoms (molecules) of basic water, yet it only saturated one atom of base, and consequently the remaining atom of water must be an integral part of the organic constituent, just as it was of ammonia in the sulphate $N_2H_5O + SO_3$.

Growth of the Radical Theory. We can now realize how matters stood when Liebig and Wöhler, in the memoir to which reference has been made, brought the first unassailable evidence of the existence of an organic compound radical. A series of substances had been obtained which were readily convertible into one another by simple reactions such as chemists were familiar with in inorganic chemistry. They contained one common group of elements $C_{14}H_{10}O_2$ to which the name *benzoyl* (*benz*, the root of benzoic, and *yl*, substance) was given. The compounds were written as follows:

$C_{14}H_{10}O_2 + H_2$	Benzoyl hydride (bitter almond oil)
$C_{14}H_{10}O_2 + O + H_2O$	Benzoic acid
$C_{14}H_{10}O_2 + Cl_2$	Benzoyl chloride

¹ *Jahresb.*, 1828, 8, 292.

² *Jahresb.*, 1833, 13, 192.

$C_{14}H_{10}O_2 + Br_2$	Benzoyl bromide
$C_{14}H_{10}O_2 + I_2$	Benzoyl iodide
$C_{14}H_{10}O_2 + N_2H_4$	Benzamide
$C_{14}H_{10}O_2 + C_2N_2$	Benzoyl cyanide
$C_{14}H_{10}O_2 + S$	Benzoyl sulphide
$C_{14}H_{10}O_2 + O + C_4H_{10}O$	Benzoic ether

This was not, however, the first example of a compound radical. In 1815 Gay-Lussac, in controlling Berthollet's experiments on the composition of hydrocyanic acid, obtained cyanogen by heating mercuric cyanide, and by the action of the halogens on hydrocyanic acid prepared the chloride, bromide, and iodide of cyanogen. This example of a compound radical, as well as that of sulphocyanogen and ammonium, were overlooked, partly because they were ranked with inorganic substances, partly because Lavoisier's original conception of a radical necessarily implied that part of a substance of which the other part was oxygen. It should be observed that in benzoyl we have a modification of Lavoisier's definition of a compound radical inasmuch as benzoyl contained oxygen.

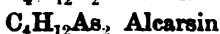
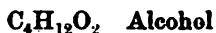
Liebig and Wöhler's discovery was soon followed by that of other radicals. The radicals of salicylic and cinnamic acids were shown, the former by Piria, and the latter by Dumas and Peligot, to form each a series of derivatives similar to that of benzoic acid, and were termed respectively *salicyl* and *cinnamyl*. Ten years later the theory of the compound radical received further confirmation in a brilliant research of Bunsen upon *cacodyl*.

In 1760 Cadet obtained by the distillation of potassium acetate with oxide of arsenic a fuming and fetid liquid, which inflamed spontaneously in the air and was extremely poisonous. It was called 'Cadet's fuming liquid'. These uninviting properties deterred chemists for seventy years from satisfying any curiosity they might have conceived as to its composition, and they contented themselves with stating its properties and method of preparation.

Dumas was the first to analyse it, and gave it the formula $C_8H_{12}As_2$; but Bunsen soon afterwards ascertained that the liquid prepared by the above method contained oxygen and had the formula $C_4H_{12}As_2O$, which he called *cacodyl oxide* (κακώδης, stinking).¹ From this he obtained, by means of the halogen acids, cacodyl chloride, bromide, iodide, and also the cyanide, fluoride, sulphide, selenide, cacodylic acid, and, finally, by the action of metallic zinc on the chloride, the

¹ Pogg., *Ann.*, 1837, 40, 219; 1837, 42, 145; *Annalen*, 1841, 37, 1; 1842, 42, 14; 1843, 46, 1; Ostwald's *Klassiker*, No. 27.

radical cacodyl itself $C_4H_{12}As_2$, which he also named *alcarsin* (alcohol-arsenic) to indicate its relation to alcohol.



He termed cacodyl a true organic element possessing the character of a metal. This analogy is readily understood if we write Kd for the cacodyl radical and compare it with a metal such as calcium.

Cacodyl	$C_4H_{12}As_2$	Kd	Ca
Cacodyl oxide	$C_4H_{12}As_2O$	KdO	CaO
Cacodyl chloride	$C_4H_{12}As_2Cl_2$	KdCl ₂	CaCl ₂
Cacodyl cyanide	$C_4H_{12}As_2Cy_2$	KdCy ₂	CaCy ₂
Cacodyl sulphide	$C_4H_{12}As_2S$	KdS	CaS

Liebig's Definition of a Compound Radical. Although this research was the product of a later period, Liebig's original definition of a compound radical has undergone no change.¹ He says, speaking of cyanogen, 'we call this a radical because (1) it is the invariable constituent of a series of compounds, (2) it can be replaced by other simple bodies, and (3) in its combinations with a simple body the latter may be substituted by equivalents of other simple bodies. Of these three conditions, two must be fulfilled.' These conditions made it essential that in a series of simple reactions the radical or group of elements should be shown to remain intact, and not only to be capable of combining with elements to form compounds, but also of being replaced by them.

It is evident from this statement that the author conceived the elements of which the radical was composed to be united by a bond which joined them together more firmly than the other elements in the compound. The particular group composing the radical upon which the choice fell was a matter of much diversity of opinion. This is specially noteworthy in the case of ether and alcohol and their derivatives.

The Radical 'Ethyl'. We have already referred to the etherin theory of Dumas and Boullay and the comparison which they drew between olefiant gas and ammonia. There existed at the time another view of the constitution of ammonia and its salts. The theory that ammonium played the part of a metallic radical in its salts was suggested by Davy, and afterwards supported by Ampère and Berzelius. It appealed to the dualists, for it enabled them to establish an analogy between the composition of the salts of ammonia.

¹ *Annalen*, 1833, 25, 2.

and those of the alkali metals. This view was now revived by Liebig, and, in place of etherin C_4H_8 and its analogue ammonia NH_3 , the new radical C_4H_{10} , termed by Liebig etheryl or ethyl¹ (*αιθήρ*, ether, and *αιλ*, substance), took its place beside ammonium.

$C_4H_{10}Cl_2$	Hydrochloric ether.	$N_2H_8Cl_2$	Ammonium chloride.
$C_4H_{10}O$	Ether.	N_2H_8O	Ammonium oxide (present in the salts).
$C_4H_{10}O + H_2O$	Alcohol.	$N_2H_8O + H_2O$	Ammonium hydrate.
$C_4H_{10}O + N_2O_5$	Nitric ether.	$N_2H_8O + N_2O_5$	Ammonium nitrate.
$C_4H_{10}O + C_4H_6O_3$	Acetic ether.	$N_2H_8O + C_4H_6O_3$	Ammonium acetate.

Berzelius who had, as we have seen, abandoned the etherin theory, accepted the new doctrine, for its basis was dualistic, inasmuch as ether appeared as an oxide. He and Liebig, however, held different views on the constitution of alcohol. Liebig regarded it, from its relation to ether, as the hydrate of ether, whereas Berzelius considered it to be the oxide of a different radical, C_2H_6 .² One reason advanced by Berzelius was the difference in properties between sulphovinic acid obtained by the action of sulphuric acid on alcohol, and isethionic acid, prepared by Magnus by the action of sulphuric acid (SO_3) on alcohol and ether.³

The two substances are isomeric and saturate the same amount of base, but the barium salt of sulphovinic acid contains an atom more water than that of isethionic acid, and they are in other respects totally distinct substances. 'It is clear, therefore,' writes Berzelius in the *Jahresbericht* for 1833, 'that this atom of water cannot be present as water of crystallization, but must be there in another form, and this other form can be nothing else than a form of ether. It naturally follows that alcohol and ether are not hydrates of the same base, although they may be so regarded.'

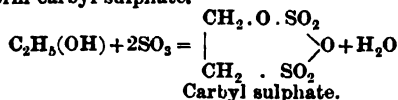
The two formulae of the barium salts would therefore appear as $2C_2H_6O + 2SO_3 + BaO$ for the sulphovinate, and $C_4H_{10}O + 2SO_3 + BaO$ for the isethionate.⁴

¹ *Annalen*, 1834, 9, 1.

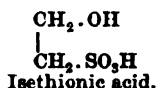
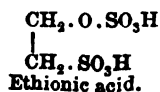
² *Jahresb.*, 1833, 13, 194.

³ *Annalen*, 1833, 6, 168; *Pogg., Ann.*, 1833, 27, 367.

⁴ According to modern views the formation of isethionic acid from ethionic acid and carbyl sulphate would be represented as follows: alcohol and sulphur trioxide unite to form carbyl sulphate.



Carbyl sulphate is decomposed by water, first into ethionic, and finally into isethionic acid:



But there were additional reasons. Berzelius contended that the dissimilarity in properties of alcohol and ether could not be attributed to the presence or absence of water. Nor was it probable that in alcohol the water could have so strong an affinity for the ether (with which in the free state it cannot be induced to combine) that a dehydrating agent, like barium oxide, can produce from alcohol no trace of ether.

Growth of Organic Chemistry, 1830-1840. Whilst the various disputants were urging the claims of rival radicals, their activity in the laboratory was not suspended. Organic chemistry was steadily advancing and widening its boundaries by new discoveries, which followed one another in rapid succession. The foundation of the great edifice of aromatic chemistry was being laid, upon which the next generation was to build new and important industries. Mitscherlich had obtained *benzene* from benzoic acid by distillation with lime, identical with Faraday's hydrocarbon from oil gas (p. 56), and formed *nitrobenzene*, *benzenesulphonic acid*, *chlorobenzene* and certain other derivatives. Runge had found *kyanol*, afterwards identified as aniline, and *carbolic acid* in coal-tar. Liebig had obtained *chloral* and *chloroform* by the action of chlorine on alcohol, and had determined the composition of *acetone*, *aldehyde*, and *acetal*. Dumas and Pellgot had isolated *methyl alcohol* in the pure state from wood spirit, and Dumas and Cahours had prepared *amyl alcohol* from fusel oil. In both cases a number of derivatives had been obtained offering a close analogy with those from ordinary alcohol. Zeise had discovered the *mercaptans*, and Regnault had studied the action of potash on Dutch liquid, and obtained the compound we now call *vinyl chloride*. The formula of the new compound was written $C_4H_6Cl_2$ and, according to Regnault, contained the radical C_4H_5 , which he termed *aldehydène*, subsequently changed to *acetyl*. In the meantime a partial reconciliation had been arrived at between Liebig and Dumas, when the latter was won over to the 'radical' views of Liebig, and the result was a joint article which appeared in 1837, and of which the following is an abstract.¹

'Organic chemistry possesses its own elements, which sometimes play the part of chlorine or oxygen (e.g. cyanogen), and sometimes that of a metal (e.g. ethyl, benzoyl, cacodyl). Cyanogen, amide, benzoyl, the radicals of ammonia, of the fats, of alcohol and its derivatives, are the true elements of organic nature, whereas the

¹ *J. prakt. Chem.*, 1837, 14, 296; *Compt. rend.*, 1837, 5, 567.

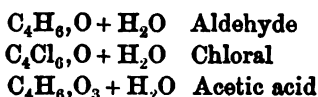
simplest constituents, carbon, hydrogen, oxygen, and nitrogen, only reappear when the organic matter is completely destroyed.'

The truce did not last long, and when the new radical, acetyl, appeared, Liebig seized upon it in order to explain the constitution of those compounds, which, like Zeise's platinum compounds and Dumas' oxamethane, contained no ethyl radical, without having recourse to the etherin theory to which he was a firm opponent. Like his predecessors he established an analogy with ammonia and its derivatives by introducing into the latter the radical *amide*.¹

Letting Ac stand for acetyl, C_4H_6 , and Ad for amide, N_2H_4 , the series of compounds appeared with the following formulae:

AcH ₂	Olefiant gas.	AdH ₂	Ammonia.
AcH ₄	Ethyl.	AdH ₄	Ammonium.
AcH ₄ O	Ether.	AdH ₄ O	Ammonium oxide.
AcH ₄ Cl ₂	Ethyl chloride.	AdH ₄ Cl ₂	Salammoniac.
AcH ₄ O + H ₂ O	Alcohol.	—	—
AcH ₄ S + H ₂ S	Mercaptan.	AdH ₄ S + H ₂ S	Ammonium sulphide.
AcH ₂ + 2SO ₃ ²	Isethionic acid.	AdH ₂ + SO ₃	Rose's anhydrous ammonium sulphate.
—	—	2Ad + 2CO	Urea.
—	—	Ad + 2CO	Oxamide.
AcH ₄ , Ad + 2C ₂ O ₃	Oxamethane.	—	—

The new theory also enabled Liebig to include in his scheme aldehyde, chloral, and acetic acid, which appeared as follows:



The introduction of the new acetyl radical C_4H_6 into alcohol and its derivatives never actually replaced the older ethyl radical which continued to be used by the German chemists, whilst etherin was retained in France.

The Chemistry of Compound Radicals. With the year 1840 the first chapter in the history of organic chemistry may be said to close. Although organic chemistry was still concerned with products of a vital force, and with the compounds derived from them by the action of chemical reagents, the dominant idea was the compound radical. It was around the compound radicals that the various organic substances were grouped. In Liebig's treatise, which was published

¹ *Annalen*, 1839, 30, 129.

² This formula represents the anhydride of the acid. After Regnault's discovery of its preparation from sulphur trioxide and olefiant gas, it was usually represented as a compound of etherin and sulphuric anhydride.

in 1840, all the well-defined compound radicals, whether containing carbon or not, are included. Separate chapters are devoted to amide, oxide of carbon (the radical of oxalic acid), cyanogen, benzoyl, cinnamyl, salicyl, ethyl, acetyl, methyl, formyl, cetyl, amyl, and glyceryl. They were hypothetical groups which might or might not be capable of separation, but their admission was a necessity and their existence in the compound more than probable. Organic chemistry was defined by Liebig as the *chemistry of the compound radical*.

Theory of Substitution. Meanwhile a movement had begun, which, gathering force as it advanced, swept away two ruling principles, the one, the electro-chemical theory, the other, the pre-existence, as it was termed, of radicals as unalterable groups of elements, or proximate constituents of organic compounds. It was the direct result of the study of a chemical process which has been termed *substitution*. The idea of substitution was not a new one. The substitution of a metallic oxide for water in an acid hydrate to form a salt, and Mitscherlich's discovery that the crystalline form of a compound is often retained when one element replaces another, were well known to chemists. Among organic compounds, the action of chlorine on hydrocyanic acid had been found by Gay-Lussac to give cyanogen chloride, Liebig and Wöhler had obtained benzoyl chloride from bitter almond oil, and Faraday prepared carbon sesquichloride, C_2Cl_3 , from Dutch liquid in the same manner.

Dumas' Law of Substitutions. In 1834 Dumas' attention had been directed to the action of chlorine on organic compounds by observing, as Gay-Lussac had previously done, that when wax is bleached by chlorine a portion of the hydrogen is replaced by chlorine. He found also that, when chlorine acts upon turpentine, for every volume of hydrogen removed an equal volume of chlorine enters. He then repeated Liebig's experiments on the action of chlorine and bleaching powder upon alcohol, and carefully analysed the products. From the result of these researches he formulated, in 1834, the following *empiric law of substitutions*.¹

1. If a body containing hydrogen be acted upon by chlorine, bromine, or iodine, or oxygen, for every atom of hydrogen which it loses, it takes up one atom of chlorine, bromine, or iodine, or half an atom of oxygen.

2. If the compound, besides hydrogen, contains oxygen, the same rule holds without modification.

¹ *Ann. Chim. Phys.*, 1834, 56, 113.

removed, the system falls to pieces. To the central prism other geometrical figures can be attached, on removing which the original form reappears. The following examples may serve to illustrate the theory. By the alternate action of chlorine and potash on olefiant gas, a number of chlorinated compounds had been obtained. These were supposed to contain the primary nucleus C_4H_8 . The compounds were written as follows, the nomenclature being that of Dumas and Peligot:

Etherène	C_4H_8
Etherène hydrochlorate (hydrochloric ether)	$C_4H_8 + H_2Cl_2$
Chlorétherase (Regnault's acetyl chloride)	$C_4H_6Cl_2$
„ hydrochlorate (Dutch liquid)	$C_4H_6Cl_2 + H_2Cl_2$
Chlorétherese	$C_4H_4Cl_4$
„ hydrochlorate	$C_4H_4Cl_4 + H_2Cl_2$
Chlorétherise	$C_4H_2Cl_6$
„ hydrochlorate	$C_4H_2Cl_6 + H_2Cl_2$
Chlorétherose	C_4Cl_8
Chloride étherosique (Faraday's sesquichloride of carbon)	$C_4Cl_8 + Cl_4$

A similar series was derived from methylene and naphthalene, whilst alcohol and its oxidation products appeared as follows:

Alcohol	$C_4H_8 + H_4O_2$
Aldehyde	$C_4H_6O + H_2O$
Acetic acid	$C_4H_4O + O_2$

Although Laurent's formulae bore a certain resemblance to those of the etherin theory, they really embodied an important new principle, namely, that when chlorine and bromine replace their equivalent of hydrogen, the former *take the place* of the latter, and play to some extent the same part in the new compound, in consequence of which the compound retains a certain similarity to the parent substance.

The theory amounted to a revolution. We cannot wonder that it should have served as a direct challenge to Berzelius and the followers of the electro-chemical school. The principle, once admitted, that chlorine, an electro-negative element, could take the place of hydrogen, an electro-positive element, and do so without changing the typical properties of the new compound, was to shake the very foundation of dualism; for we must remember that it was this opposite negative and positive character which served to link the atomic units in a compound; it was this dual conception which saw a new hydro-carbon radical in every compound in which hydrogen was replaced by another element.

Berzelius was not slow in replying. His first contemptuous comment on the new formulae of Laurent appeared in his *Jahresbericht* for 1887: 'I consider it superfluous to enlarge further on such a theory.' He then directed his attack against Dumas, who at once repudiated the revolutionary views of Laurent:¹ 'To represent me as saying that when chlorine replaces hydrogen it plays the part of the hydrogen, is to attribute to me an opinion against which I strongly protest, as it is opposed to everything I have written on this subject. The substitution theory expresses only the relation which exists between the hydrogen which disappears and the chlorine which takes its place,' and further on, 'It is an empiric rule which is of value so long as it holds; if any one has given it an extension which was not in my mind, I am not responsible.' When, however, Dumas afterwards (1889) obtained trichloroacetic acid by passing chlorine into acetic acid, and found that the new compound not only retained the characteristic acid property of the original substance, saturating the same amount of base and forming salts and esters, but yielded chloroform with potash, as acetic acid yielded marsh gas, the analogy between the two was complete, and Dumas henceforth participated in Laurent's views.

'It is clear,' wrote Dumas, 'that if I accept this doctrine, which is based upon facts, I cannot attach any weight to an electro-chemical theory which has been the dominant idea upon which Berzelius has sought to construct a universal system.'

'But these electro-chemical ideas, this special polarity which is assigned to the atoms of simple bodies, do they rest upon such clear facts that they may rank as articles of faith? Or, if they are considered as hypotheses, have they the property of adapting themselves to the facts with such certainty that they can be utilized in chemical investigations? It must be conceded that such is not the case.'

'Isomorphism—a theory based upon facts—has been a true guide in mineral chemistry, and, as is well known, has little in common with electro-chemical theories.'

'Now, in organic chemistry, the theory of substitution plays the same part as isomorphism in inorganic chemistry, and indeed it may happen that future experience will show that both views are related and spring from the same cause, which may be combined in a common expression.'

'For the present, from the conversion of acetic into chloroacetic acid and from that of aldehyde into chloral, from the fact that the

¹ *Compt. rend.*, 1888, 6, 699.

whole of the hydrogen is replaced by chlorine, volume for volume, without changing their original nature we must conclude:

'That there exist in organic chemistry certain types which remain as such even after their hydrogen has been replaced by an equal volume of chlorine, bromine, or iodine.'

'That is to say, the theory of substitution rests on facts, and on the most striking facts, of organic chemistry.'

Dumas' Theory of Types. Dumas' *Theory of Types* incorporated his former law of substitutions and Laurent's propositions under a somewhat modified form.¹

The new theory was introduced in order to emphasize the difference between the substituted compound and the parent substance in which the general character or type was preserved, as in the case of acetic and chloracetic acid or aldehyde and chloral, on the one hand, and, on the other, those substitution products (more especially where oxygen replaced hydrogen) which were not related by similarity of properties as exemplified by alcohol and acetic acid or marsh gas and formic acid. The former belonged to the same *chemical* type and the latter to a *mechanical* or *molecular* type.

The two groups may be illustrated by the following examples, using Dumas' notation:

<i>Chemical type.</i>		<i>Mechanical type.</i>	
Acetic acid	$C_2H_4H_2O_4$	Alcohol	$C_2H_6H_2O_2$
Chloracetic acid	$C_2H_3Cl_2O_4$	Acetic acid	$C_2H_4H_2O_4$
Aldehyde	$C_2H_4H_2O_2$	Marsh gas	$C_2H_2H_4$
Chloral	$C_2H_3Cl_2O_2$	Formic acid	$C_2H_2O_2$

Dumas pointed out that the properties of a compound lay in the arrangement of its atoms and not in their nature. He wrote: 'Lavoisier's compounds were a combination of a combustible element with a combustion supporting element. The electro-chemical theory saw in these an electro-negative and an electro-positive element, which is a modification of the same thing. This dualism is unnecessary to explain the constitution of chemical compounds, the parts of which may be compared to those of a planetary system which are held together by mutual attraction. They may be more or less numerous, simple or complex. In the constitution of the compound they play the same part as the simple elements, Mars or Venus, in our planetary system, the atomic group Earth with its moon, or Jupiter with its satellites. If in such a system one part is replaced by another of a different kind, equilibrium is maintained, and, if the replaced and

¹ *Ann. Chim. Phys.*, 1840, (2), 78, 78.

replacing elements resemble one another, the new compound has similar chemical properties to the original one. If, however, they differ they belong to a mechanical system, and the chemical similarity is difficult to recognize.'

There was a tendency to carry this theory of substitution too far, and when Dumas suggested that even carbon might undergo substitution¹ the idea was ridiculed by Liebig.²

In the meantime Liebig had himself contributed to the overthrow of the electro-chemical theory.

The Constitution of Organic Acids. Liebig published in 1838³ a paper 'On the Constitution of Organic Acids'.

The organic acids, it must be remembered, were the only class of substances which had representatives of a strictly analogous character among inorganic compounds, and any new theories respecting the structure of the latter would necessarily include organic acids. Before discussing the subject of Liebig's paper, it may be well to gain some idea of the views generally held in regard to the constitution of acids and salts. In inorganic chemistry salts of oxyacids were assumed to be compounds of non-metallic oxides (called acids) with metallic oxides or bases. What we now term acid was the hydrate, the water being sometimes termed basic water, which indicated that in the formation of salts it was replaceable by a base. The same principle was applied to organic acids and salts, C_2O_3 standing for oxalic acid and $C_4H_2O_3$ for acetic acid, as already pointed out (p. 7). The molecular weight of an acid was derived from the neutral salts, which were assumed to contain one equivalent of base united to one of acid. Thus, sulphuric acid and the sulphates were written $SO_3 + H_2O$, $SO_3 + KO$, $SO_3 + AgO$, $SO_3 + CaO$, &c. An acid salt was a neutral salt combined with an equivalent of hydrated acid; a basic salt was a neutral salt with an additional equivalent of base. Bisulphate of potash, as it was then called, had the formula $SO_3 \cdot H_2O + SO_3 \cdot KO$. The molecular weight of an organic acid, like citric acid, was determined from its silver or lead salt. According to Berzelius $C_4H_4O_4 + AgO$ was the silver salt of citric acid, $C_4H_4O_4 + H_2O$ was the acid hydrate, and $C_4H_4O_4$ stood for the acid.⁴ The varying basicity of acids was not recognized.

There was one exception to the above rules. In ordinary sodium phosphate the ratio of one equivalent of base to one of acid would

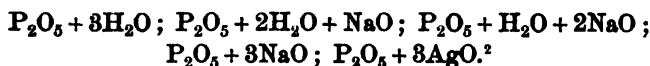
¹ *J. prakt. Chem.*, 20, 281.

² *Annalen*, 1840, 33, 308.

³ *Annalen*, 1838, 26, 113; Ostwald's *Klassiker*, No. 26.

⁴ These formulae are obviously incorrect. The correct formula of the acid hydrate determined by the method described would be $C_4H_4O_4 + H_2O_2$.

give the formula (leaving out water) $\text{PO}_{24} + \text{NaO}$, and this was therefore altered to $\text{P}_2\text{O}_5 + 2\text{NaO}$. The additional molecule of water, which we now recognize as forming a part of the compound, was included in the total water of crystallization. But a curious anomaly was discovered by Clark. In attempting to prepare anhydrous sodium phosphate he found that the ordinary crystalline phosphate loses water on heating, but forms a new salt, which has properties entirely distinct from common sodium phosphate, and does not unite at once with water to form the original compound.¹ The explanation was given by Graham. He showed that there exists in phosphoric acid three molecules of water, which are replaceable by one, two, or three molecules of base as follows:



He distinguished between the three molecules of combined water and the water of crystallization. When the water of crystallization is expelled no change in chemical properties results; but if the temperature is raised so as to drive off the combined water, then salts of new acids are formed. He prepared in this way the sodium salts of pyro- and meta-phosphoric acids and the acids themselves by heating ordinary phosphoric acid. Graham proved in this way that, whereas ordinary phosphoric acid has three replaceable atoms of water and is therefore tribasic, pyrophosphoric acid contains two and is dibasic, and metaphosphoric acid only one, and is therefore monobasic.

Liebig carried these researches into the field of organic chemistry. He found, for example, that citric acid, like phosphoric acid, formed three series of salts, and that the analysis of the acid dried at 100° did not agree with the formula of Berzelius, but must be represented by $\text{C}_{12}\text{H}_{10}\text{O}_{11} + 3\text{H}_2\text{O}$. The analogy between phosphoric and citric acid could be carried even further, for citric acid on heating loses water and is converted into pyrocitric acid (citraconic acid), which is dibasic. The old rule for determining the molecular weight of an acid as the quantity, which saturates one equivalent of base, had to be relinquished, and it now became necessary to fix beforehand the basicity of the acid before the weight of the molecule could be ascertained. Liebig's rule was to find, in the first instance, whether the acid was capable of uniting with more than one kind of base. Thus tartaric acid was dibasic, as it formed, in the case of Rochelle salt

¹ *Phil. Trans.*, 1833, 2, 280.

² The equivalent notation in which phosphorus had double its present combining weight represented phosphoric acid as PO_6 .

and tartar emetic, a tartrate of potash and soda, and of potash and antimony oxide. Sulphuric acid, on the other hand, remained monobasic, because a sulphate with two bases was unknown. The acid sulphates continued to be written as a double molecule of acid and neutral salt.

At the close of the paper Liebig reviews the whole question of the presence of water in acids. He saw that the separation of water by the action of a base on an acid is an insufficient explanation, for the oxygen of the water may be conceived as coming from the metallic oxide just as well as existing already combined in the acid hydrate. Moreover, in the case of organic acids the presence of water is improbable, since the anhydrous acids are purely fictitious entities, having never been isolated.

Liebig revived the theory of Davy (1809) and Dulong (1819) in regarding acids as compounds of hydrogen,¹ and he pointed out, as they had done, that it was illogical to separate the halogen acids, hydrocyanic acid, and hydrogen sulphide from the oxyacids by an artificial barrier. He further contended that if, for example, silver sulphocyanide is $\text{Cy}_2\text{S} + \text{SAg}$, the silver, being already present as sulphide, should not separate in this form when hydrogen sulphide acts upon the salt, but the reverse actually happens; if, then, silver sulphocyanide is $\text{Cy}_2\text{S}_2 + \text{Ag}$ and the sulphocyanic acid is $\text{Cy}_2\text{S}_2 + \text{H}_2$, then cyanic acid must be $\text{Cy}_2\text{O}_2 + \text{H}_2$, and so on with the other acids.

The conception of acids as compounds of hydrogen did not at once replace the older view, but by affording a simple and legitimate interpretation of the formation of salts from acids by the substitution of hydrogen by a metal, it threw doubt on the validity of the electro-chemical theory.

Gerhardt and Laurent. The theory of polybasic acids was subsequently modified and expanded by Charles Gerhardt and Auguste Laurent, two chemists whose names will always be linked together in the history of chemical science. They were essentially reformers, and, like many ardent reformers, they relentlessly threw over time-honoured formulas and rode rough-shod over cherished traditions. In their place they set up empiric rules of classification and artificial systems of notation and nomenclature which were

¹ Davy supported his view on the ground that potassium chlorate parts with its oxygen on heating and forms potassium chloride, and concluded that this stronger affinity of the metal for the acid than for oxygen must also obtain among the oxyacids. Dulong based his opinion on the constitution of the oxalates, which he regarded as carbon dioxide united to the metal, thus: $2\text{CO}_2 + \text{Pb}$ and oxalic acid $2\text{CO}_2 + \text{H}_2$.

difficult to understand or assimilate. They thus alienated the sympathy of their fellow chemists, who treated them in a manner now painful to contemplate. Although no action on the part of Gerhardt and Laurent justified such treatment, yet it must be confessed that had they adopted a less uncompromising attitude towards men who were their seniors in years and reputation, it would have gone far to soften the asperities of a situation which they unfortunately helped to create.¹

The Unitary System. Gerhardt and Laurent clearly saw the confusion into which the electro-chemical theory had plunged organic chemistry, and they set themselves resolutely to extricate it from the network of vague and unprofitable speculations in which it had become involved. In Laurent's preface to his *Chemical Method*² he writes: 'The confusion which reigns in the ideas is even greater than that which obtains in the facts; for the principles upon which the majority of chemists rely for the explanation and co-ordination of facts are so vague, so uncertain, that not only do two chemists explain the same phenomena in two different ways, but even one and the same person abandons an explanation he gave yesterday for a new one he proposes to-day, and which he will abandon to-morrow for a third.' Gerhardt, in his *Précis de chimie organique* (1844), says much the same thing: 'When a chemist at the present time observes a reaction or analyses a new substance his first care is to conceive a little theory which shall explain the phenomena according to electro-chemical principles, and it is customary to create a hypothetical radical in order to adapt these principles to the new compound'; and again, 'Six or seven formulæ have been suggested for alcohol, each observer trying to support his own; but after all, each of these formulæ is but the expression of one or two reactions. Upon one thing only are we agreed, and that is the empiric formula for alcohol.' They laid aside the electro-chemical theory and the doctrine of the compound radical as fixed, proximate constituents. Organic compounds were no longer binary compounds, nor an arrangement of certain fixed groups of elements. They were, as Dumas expressed it, *édifices simples*, simple structures, in which one or more elements might be replaced by others. In opposition to the binary or dualistic principle the system was termed *unitary*. Reactions were expressed by equations, but not in the customary fashion, for they did not, by introducing radicals, formulate any preconceived internal structure of

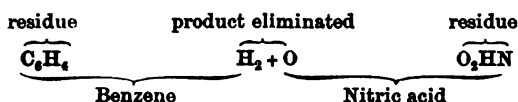
¹ *Vie de Charles Gerhardt*, by Grimaux and Gerhardt, Masson & C^o, Paris, 1900.

² *Chemical Method*, by A. Laurent, trans. by W. Odling, Cavendish Society's Publications, London, 1855.

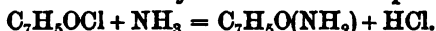
the substances taking part, but merely indicated the interchange of constituents. The interchange was ascribed to the stability of such combinations as water, hydrochloric acid, carbonic acid, and ammonia, which, though they might be eliminated in the process, did not therefore pre-exist in any of the reacting substances. The new compound was formed by a double decomposition accompanied by the removal of a part of the reagent, in combination with part of the reacting substance, and the residues or *restants* then united.

Gerhardt's Theory of Residues. This embodied the principle of Gerhardt's system of residues and copulated compounds which appeared in 1839.¹ The fundamental idea was that of substitution, for, according to Gerhardt's rule, 'the element which is removed is replaced by the equivalent of another element or by the residue of the reacting substance.'

Gerhardt represented the action of nitric acid on benzene thus:



The residue HNO_2 replaced the atoms of hydrogen in benzene. The action of ammonia on benzoyl chloride was expressed in a similar way:



Chlorine is removed from benzoyl chloride and hydrogen from ammonia, and the two residues unite to form benzamide.

Conjugated Compounds. The introduction of the term *copula* or *conjunct* arose in the following way: the action of nitric acid on benzene, or sulphuric acid on alcohol has no parallel in that of an acid on a base in inorganic chemistry, except that water is removed. Nitrobenzene is not a salt, for the acid and base cannot be replaced by other acids or bases, and in sulphovinic acid and the sulphonic acids the sulphuric acid can no longer be detected by ordinary reagents. The original constituents are completely masked and the residues may have their atoms differently arranged. They are, as Dumas expressed it, in a *form of substitution*.² The action of nitric acid on benzene can be represented as a substitution, as already pointed out, but not that of sulphuric acid on a hydrocarbon or alcohol, for the saturation capacity of the acid, according to the formulae then in use, remains unchanged. Different bases may

¹ *Ann. Chim. Phys.*, 1839, 72, 180.

² This *form of substitution* bears a close resemblance to non-ionisable compounds.

saturate the acid, but the organic constituent remains permanently attached. This indifferent residue which was attached to the acid was called by Gerhardt¹ the copula and gave rise to the term *copulated compounds* (sels copulés), which, however, very soon lost its original meaning. When the different basicities of the acids was recognized and sulphuric acid became in Gerhardt's system dibasic then the term copulated compound or *conjugated compound*, as it was called by Dumas, received the following interpretation:² 'The basicity or saturation capacity of a conjugated compound is always less by one unit than the sum of the basicities belonging to the two original substances.' Thus benzenesulphonic acid, obtained from benzene and sulphuric acid, is monobasic, whilst benzenesulphobenzoic acid, which is formed from benzoic acid and sulphuric acid, making a total of three units of basicity, is dibasic. When the majority of organic compounds with acids was embraced by the term conjugated, this rule was applied to determine the basicities of acids. It was taken as a proof that nitric acid was monobasic because it formed a neutral compound with benzene.

Formulae of Gerhardt and Laurent. The attempt to attach to the terms atom, molecule, volume, and equivalent a definite and logical meaning and to establish a rational system of chemical formulae was one of the most important services rendered by Gerhardt and Laurent to chemical science. It has already been stated that the different opinions which existed on the interpretation and in the application of these expressions, was such that many chemists had renounced the atomic system of Berzelius and taken refuge in Gmelin's equivalent notation. Their troubles were not at an end and difficulties still pursued them. It could scarcely be otherwise so long as the molecule remained an indefinite quantity.

Gerhardt³ introduced a new principle. Reviving Avogadro's law, though in a somewhat restricted sense, he proposed to make the equivalents, by which he implied molecules, of all volatile compounds and gases correspond to equal volumes. For this reason he reinstated Berzelius' old formula H_2O for water, seeing that it was composed of two volumes of hydrogen and one of oxygen. From the density of mercury vapour, mercuric oxide received the formula Hg_2O in place of HgO , and the other basic oxides were referred to the same general type M_2O . The result was that the atomic weights of all

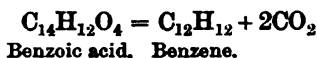
¹ *Ann. Chim. Phys.*, 1839, 72, 186; Gmelin's *Handbook*, 7, 213.

² *Précis de Chimie Organique*, I, 98; Laurent's *Chemical Method*, p. 211.

³ *Précis de Chimie Organique*, I, 52.

the metals were halved, whereby only the alkali metals and silver received their present values.

Law of Even Numbers. In his original memoir published in 1842 Gerhardt¹ determined the molecular weight by taking the weight of four volumes of vapour (compared with one of hydrogen). Finding that by so doing the number of molecules of water or carbonic acid removed in a chemical decomposition was always even, he proposed to double the molecular weights of these substances whereby they would become equivalent to ammonia N_3H_6 and correspond to four volumes. The decomposition of benzoic acid into benzene or of lactic acid into lactide were usually represented as follows:



It naturally followed that every organic compound contained an even number of carbon atoms, which suggested to Gerhardt and Laurent the idea embodied in their empiric 'law of even numbers', according to which the sum of the carbon and oxygen atoms on the one hand and of hydrogen, the halogens, metal and nitrogen, on the other, was divisible by 2.

These views were very soon modified. In the *Précis de Chimie Organique* already referred to, in place of four volumes the two volume basis of molecular weights is adopted, and all the formulae are halved. Hydrochloric acid, ammonia and water appear as HCl , NH_3 and H_2O , ether is $C_4H_{10}O$ and alcohol C_2H_6O , &c. The Law of Even Numbers was restricted to the sum of the hydrogen halogens, nitrogen, phosphorus and arsenic atoms. The law still holds, and depends on the quadrivalency of carbon. Though at the time purely empirical, it had the effect of drawing attention to many formulae, which proved to be inaccurate and which were corrected and simplified.

Basicity of Acids. The halving of the atomic weights of the metals and the introduction of the two volume standard of molecular weights, brought out clearly the relation between related compounds. Acetic acid was now written $C_2H_4O_2$ and silver acetate $C_2H_3AgO_2$, oxalic acid was $C_2H_2O_4$ and silver oxalate $C_2Ag_2O_4$. The basicity of the acid appeared as the number of hydrogen atoms replaceable by

¹ *Revue scientifique de Queneville*, 1872.

a metal, and *basic water* necessarily vanished. The series were written as follows:

<i>Monobasic.</i>	<i>Dibasic.</i>	<i>Tribasic.</i>
Nitric acid $\text{NO}_3 \cdot \text{H}$	Sulphuric acid $\text{SO}_4 \cdot \text{H}_2$	Phosphoric acid $\text{PO}_4 \cdot \text{H}_3$
Formic „ $\text{CHO}_2 \cdot \text{H}$	Oxalic „ $\text{C}_2\text{O}_4 \cdot \text{H}_2$	Citric „ $\text{C}_6\text{H}_5\text{O}_7 \cdot \text{H}_3$
Acetic „ $\text{C}_2\text{H}_3\text{O}_2 \cdot \text{H}$		

Other criteria of basicity were afterwards added by Gerhardt and Laurent. It was no longer essential that an acid to be dibasic should form a double salt with two different bases, as defined by Liebig (p. 23). An acid, if monobasic, formed one salt, one ether and one neutral amide. It was dibasic if it formed an acid and neutral salt, an acid and neutral ether and an acid and neutral amide, as well as an acid chloride containing two atoms of chlorine.

Sulphuric acid and oxalic acid were consequently dibasic and formed the following series of derivatives:¹

Oxalic acid	$\text{C}_2\text{O}_4 \cdot \text{H}_2$	Sulphuric acid	$\text{SO}_4 \cdot \text{H}_2$
Potassium ethyl oxalate	$\text{C}_2\text{O}_4(\text{C}_2\text{H}_5)_2\text{K}$	Potassium sulphate	$\text{SO}_4 \cdot \text{K}_2$
Diethyl oxalate	$\text{C}_2\text{O}_4(\text{C}_2\text{H}_5)_2$	Potassium bisulphate	$\text{SO}_4 \cdot \text{KH}$
Oxamide	$\text{C}_2\text{O}_4(\text{NH}_2)_2$	Sulphovinic acid	$\text{SO}_4(\text{C}_2\text{H}_5)\text{H}$
Oxamic acid	$\text{C}_2\text{O}_4(\text{NH}_2)\text{H}$	Ethyl sulphate	$\text{SO}_4(\text{C}_2\text{H}_5)_2$

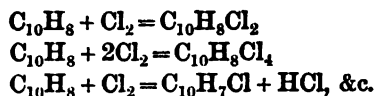
The radicals, at first entirely discarded by Gerhardt, were afterwards introduced into his residues. It was clear that in a substance like acetic ether some kind of fixity existed between the constituent parts, acetic acid and alcohol, from which it was obtained and into which it could easily be converted.

Gerhardt's System of Classification. We cannot conclude an account of Gerhardt's contributions to organic chemistry without a brief reference to his system of classification which appeared in the *Précis* of 1844. He begins by defining organic chemistry as *the chemistry of carbon compounds*, and proceeds to show how living nature has elaborated the most complex of these substances, the simpler ones being products of their decomposition. The latter may be obtained artificially; but the chemist has not yet succeeded in building up the former. He then proceeds to explain how a simple classification may be obtained by arranging compounds having similar properties according to the number of carbon atoms which they contain, and which he termed *échelle de combustion*. In the different series the carbon and hydrogen appear in the ratio of one to two. Expanding an idea which Dumas had applied to the organic acids, and Schiel (1842) to the alcohols, Gerhardt pointed out that if *R* stands for this ratio, then marsh gas and the paraffin series are

¹ Laurent's *Chemical Method* (Eng. trans.), 61, 76, and 225.

represented by R^{+2} , the alcohols by $R^{+2}O$, and the acids by RO^2 , &c. To these series he gave the name of *corps homologues*. He arranged all organic compounds according to the number of their carbon atoms on the same rung of his 'ladder', and called it a *family*.

Laurent's Atoms, Molecules, and Equivalents. In his new system Gerhardt regarded as synonymous the terms atom, equivalent, and volume, by which he understood what we now express by the word *molecule*. Laurent¹ drew clearer distinctions between them. An equivalent, he stated, was a number which in addition to indicating the combining weight also expressed a function of an element. Thus, the quantity of different bases required to neutralize the same quantity of acid is its equivalent. The quantity of oxygen which replaces hydrogen in a compound is its equivalent, but this does not imply an equal number of atoms; for it is generally found that an atom of oxygen will replace two atoms of hydrogen. These equivalents are not easy to determine; for different groups of elements have frequently entirely different functions, which cannot be directly compared. Manganese in the manganous salts is equivalent to calcium; in the manganates it is equivalent to sulphur (as in the sulphates); and in the permanganates to chlorine (as in the perchlorates). But if, he said, we assume that equal volumes contain an equal number of atoms (molecules), the atoms become strictly comparable quantities independent of the function of the elements they contain. In reactions with chlorine Laurent observed that the atoms taking part are invariably an even number. Thus, from naphthalene and chlorine new products are formed both by addition and substitution:



Adopting the suggestion made by Ampère that the atoms of hydrogen and chlorine are divisible,² he concluded that the elementary gases are composed of two atoms, and he then formulated the distinction between atoms and molecules, which had been pointed out so clearly forty years before by Avogadro and Ampère, and which we still accept. When atoms of hydrogen and chlorine unite they do not simply become attached; but the molecules of hydrogen and chlorine first divide into atoms:



It was then no longer necessary to distinguish, as Gerhardt had

¹ *Chemical Method*, p. 7.

² *Chemical Method*, p. 65.

done, between the atoms of elementary gases, which were determined from the weight of single volumes, and those of volatile compounds, which were fixed by the ratio of two volumes to one of hydrogen. The molecules of all gases could now be brought into line and determined on the two volume basis. It was considerations of this nature, as well as the law of even numbers, which suggested to Laurent the formula Cy_2 for free cyanogen, instead of Cy , and $(CH_2)_2$ for that of the newly discovered radical methyl in place of CH_3 .

In spite of views thus clearly expressed and fully endorsed by both Laurent and Gerhardt, it is curious to find in Gerhardt's treatise on Organic Chemistry, the first volume of which appeared in 1853, the reappearance of the atomic weights and barred symbols of Berzelius, an account of the new system being relegated to the last volume of the book. The strong prejudice which still existed in favour of the old notation is evident from Gerhardt's reply to Pebal who questioned him on the subject: 'My book would never have found a purchaser.'¹ The new system made few converts until after the appearance of the celebrated brochure of Cannizzaro in 1858,² in which the principle of determining molecular weights by means of the vapour density was systematically laid down and logically carried through. Until that time the equivalent notation of Gmelin became almost universal.

We must interrupt the narrative at this point in order to follow the fortunes of Berzelius and his followers, who still adhered to the *radical theory*, as it was termed, in opposition to the *theory of substitution*.

The School of Berzelius. After a masterly criticism of Dumas' theory of types,³ Berzelius drifted entirely away from the French school, which now claimed Liebig and a growing number of the younger German chemists among its adherents. Nothing could shake his faith in the electro-chemical theory to which he clung more firmly than ever.

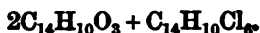
Reviving Lavoisier's definition of a radical, Berzelius wrote: 'An oxide cannot be a radical. The very meaning of the word indicates that it is the body which is united to oxygen. To regard a radical as an oxide would be equivalent to supposing that sulphurous acid (SO_2) is the radical of sulphuric acid, and manganese peroxide (MnO_2) that of manganic acid.'

¹ Ostwald's *Klassiker*, No. 30, p. 56, footnote.

² *Nuovo Cimento*, 1858, vol. vii.

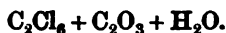
³ *Jahresb.*, 1840, 20, 260.

As only carbon, hydrogen and nitrogen could form part of an electro-positive radical, chlorine as well as oxygen had to disappear from the radical. Benzoyl $C_{14}H_{10}O_2$, the radical of benzoic acid, originally accepted by Berzelius, was now replaced by 'picramyl' $C_{14}H_{10}$, and the chlorine substitution products were explained as chlorides of hydrocarbon radicals. A difficulty was presented by bodies which contained both chlorine and oxygen. In such cases it became necessary to double and sometimes to treble the original formula. This led to the introduction of the copula or conjunct (*Paarling*), an expression borrowed from Gerhardt, but employed in an entirely different sense. Thus, phosgene was written $CO_2 + CCl_4$, that is a compound of oxide of carbon united to the conjunct, chloride of carbon. For the same reason benzoyl chloride became:

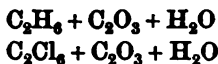


Thus Berzelius continued laboriously to construct his electro-chemical formulae upon a foundation which every moment became more insecure.¹

Chloracetic acid and acetic acid were at first regarded by Berzelius as distinct and unrelated, acetic acid being the trioxide of acetyl C_2H_3 , whereas chloracetic acid was oxalic acid united to the conjunct, chloride of carbon,



The complete analogy shown to exist between the properties of the two substances (p. 20) and Melsens' discovery (1842), that chloracetic acid can be converted by reduction with potassium amalgam and water into acetic acid, removed this shadowy distinction, and both substances now appeared as conjugated compounds of oxalic acid, one containing the radical methyl C_2H_3 , and the other chloride of carbon C_2Cl_3 :



The replacement of hydrogen by chlorine in the conjunct did not, according to Berzelius, materially affect the properties of the compound.

Still the one compound was virtually, although not admittedly, a substitution product of the other. In his satisfaction in the conjunct he had sacrificed the integrity of the radical and tacitly accepted the principle of substitution.

In 1845, Hofmann announced the discovery of the chlorinated

¹ *Jahresb.*, 1839, 19, 375.

and brominated anilines,¹ and later the iodo-, cyano- and nitro-anilines, which still retained the basic character of the original compound, although the property was weakened in proportion to the amount of hydrogen replaced. Berzelius explained the change by representing aniline, as he represented the alkaloids, as ammonia conjugated with a hydrocarbon $C_{12}H_8 + N_2H_6$; chloraniline would then be ammonia attached to the conjunct $C_{12}H_6Cl_2$. This view was at first accepted by Hofmann,² but he soon found a difficulty in explaining the anomalous behaviour of aniline oxalate, written $N_2H_6(C_{12}H_8)H_2C_2O_4$, which, unlike ammonium oxalate, refused to yield a cyanogen derivative on heating. This anomaly is removed if aniline is an amido compound; for if water is eliminated from $(C_{12}H_{10})H_4N_2 \cdot H_2C_2O_4$ the radical phenyl $C_{12}H_{10}$ must be destroyed.³

Thus aniline and its derivatives took rank as phenyl substitution products of ammonia.

In spite of the rapidly accumulating evidence in favour of the substitution theory, Berzelius never relinquished the electro-chemical theory which he had so carefully constructed and so warmly defended.

In the *Treatise* of 1827 he prophetically wrote: 'An opinion long held often brings conviction of its truth. It hides from us its weaker points, and thereby renders us incapable of accepting adverse views.'⁴ Yet nothing could be more unjust than to infer that the views of Berzelius, misleading as they proved, were unproductive.

The Researches of Frankland and Kolbe. Two disciples of his school, Frankland and Kolbe, contributed between the years 1840 and 1850 a series of researches of supreme importance to organic chemistry, which now rank among the classics of chemical literature. Kolbe's opinions were influenced by the results of his first important investigation (1844) on the action of moist chlorine on carbon bisulphide;⁵ for it is here that the galvanic battery is first mentioned 'as perhaps affording the experimenter a powerful instrument for disclosing the chemical constitution of organic compounds'. The reaction in question gave rise to a product, which was decomposed by potash, forming trichloromethylhyposulphuric acid (trichloromethylsulphonic acid). By the successive replacement of chlorine

¹ *Chem. Soc. Memoirs*, 1845, 2, 266; *Annalen*, 1845, 53, 1; 54, 23.

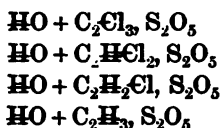
² *Annalen*, 1848, 67, 172.

³ Armstrong, *Memorial Lecture, Chem. Soc. J.*, 1893, 655.

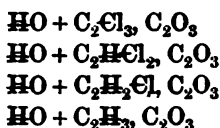
⁴ *Treatise* (1827), vol. iii, p. 50.

⁵ *Annalen*, 1845, 54, 145.

by hydrogen Kolbe obtained a series of compounds which in the barred notation of Berzelius appeared as follows:



The compounds were represented by hyposulphuric acid conjugated with methyl or substituted methyl radicals, forming a parallel series with acetic and chloroacetic acids:



'The following facts,' he concludes, 'stand in a certain relation to the new theory of substitution, and appear at first sight to lend it powerful support.'

Whilst formally admitting the principle of substitution,¹ Kolbe maintained an unshaken faith in the radicals as proximate constituents of organic compounds, which, however, can undergo substitution by chlorine, bromine, amide, nitrogen peroxide, &c., and the object of many of his polemical writings was to rehabilitate the radical theory when the rival type theory of Gerhardt, to which reference will shortly be made, threatened to replace it.

It was in the attempt to isolate the radicals that Kolbe and Frankland discovered the first general synthetic methods for preparing the paraffins. As far back as 1834 Liebig had suggested the possibility of isolating the radicals, and even suggested a method for doing so.² In 1839 Löwig announced the separation of ethyl C_4H_5 by the action of potassium on ethyl chloride,³ but it is improbable that the substance he describes was the compound in question. By acting upon ethyl cyanide with potassium Frankland and Kolbe hoped to remove the cyanogen and liberate ethyl.⁴ A gas was evolved which corresponded in composition to the radical methyl C_2H_3 .⁵ In the expectation of preparing methyl chloride they treated the gas with chlorine, and obtained a compound which could be liquefied under pressure, and had the composition $\text{C}_4\text{H}_5\text{Cl}$. The substance was in fact ethyl chloride, and the hydrocarbon, from

¹ *Annalen*, 1845, 54, 187.

² *Annalen*, 1834, 9, 15.

³ *Annalen*, 1848, 65, 269.

⁴ This was explained by supposing ethyl C_4H_5 to break up into methyl C_2H_3 and olefiant gas C_2H_2 .

⁵ *Annalen*, 1850, 75, 214.

⁶ *Pogg., Ann.*, 1839, 45, 846.

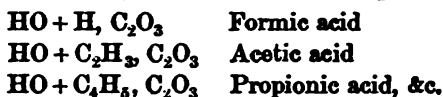
which it was obtained, ethane; but, by some alleged discrepancy in properties, the true nature of the reaction escaped them, and the chloride was described as a conjugated compound of methyl with chloromethyl $C_2H_3 \cdot C_2H_2Cl$.

Other hydrocarbons, and the first of the highly interesting class of organo-metallic compounds, were afterwards obtained by Frankland,¹ who, in continuation of the same line of investigation, substituted the iodides of the radicals for the cyanides and zinc for potassium. By the action of zinc on ethyl iodide a hydrocarbon was obtained, which was looked upon as the free radical, written now without barred atoms, C_4H_5 ,² whilst zinc, ethyl iodide and water, when heated under pressure, gave a hydrocarbon which was identical with that previously obtained by Frankland and Kolbe from ethyl cyanide and potassium, and was consequently methyl C_2H_3 . Then followed the discovery of zinc methyl, zinc ethyl, &c., and the corresponding tin and mercury compounds and their oxides, whilst Löwig and Schweizer³ succeeded in obtaining the antimony derivatives, Wanklyn⁴ discovered potassium and sodium ethyl, and Friedel and Crafts,⁵ silicon ethyl.

Not the least important of the contributions made by Kolbe and Frankland to organic chemistry, was the discovery of the synthesis of organic acids from the cyanides of the radicals.⁶ This research was again suggested by Berzelius' views on the constitution of acetic acid, which represented it as oxalic acid conjugated with methyl.

It was well known that cyanogen in aqueous solution gradually changed to the ammonium salt of oxalic acid and that hydrocyanic acid could be converted by alkalis into formic acid, which was written as oxalic acid conjugated with hydrogen H , $C_2O_3 + HO$.

It naturally followed that methyl cyanide should yield methyl oxalic acid, i. e. acetic acid, and so with the other cyanides. The experimental results fully corroborated these conclusions. Moreover, it brought out clearly the relationship of the acids as a series of hydrocarbon radicals having a group C_2O_3 , HO in common, which translated into our present notation corresponds to carboxyl:



¹ *Quart. J. Chem. Soc.*, 1849, 2, 263; *Annalen*, 1849, 71, 171.

² Although Kolbe used the barred atoms in his formulae, and continued to do so as late as 1850, they were dropped by the majority of chemists, who employed only the equivalent notation ($C = 6$; $O = 8$, &c.). To avoid confusion the barred atom is henceforth omitted in all the formulae.

³ *Annalen*, 1850, 75, 315.

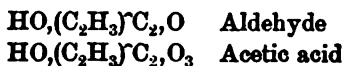
⁴ *Annalen*, 1858, 108, 67.

⁵ *Annalen*, 1863, 127, 31.

⁶ *Annalen*, 1848, 65, 288.

In direct relation to this research stands Kolbe's investigation into the behaviour of the fatty acids on electrolysis, which resulted in the discovery of a new synthesis of the paraffins.¹ It arose out of an attempt to oxidize the oxalic acid of the acids to carbon dioxide in the hope of liberating the radical with which it was united; or in his own words, 'Starting from the hypothesis that acetic acid is a conjugated compound of oxalic acid and the conjunct methyl, I considered it, under these circumstances, not at all improbable that electrolysis might effect a separation of its conjugated constituents, and that in consequence of a simultaneous decomposition of water, carbonic acid as a product of the oxidation of oxalic acid might appear at the positive, while methyl, in combination with hydrogen, viz. as marsh gas, would be observed at the negative pole.' Although the process did not take place quite in the manner anticipated, the success of the experiments is too well known to be recapitulated in detail. The radical methyl C_2H_3 (in reality ethane) was supposed to be liberated from acetic acid, and valyl C_8H_9 (in reality octane) from valeric acid.² The idea of the copula or conjunct which was requisitioned by Berzelius to divide or duplicate his formulae for dualistic purposes, received from Kolbe a rather more definite signification than Berzelius had attached to it, and led to very interesting developments.

If all the organic acids are conjugated oxalic acids, it follows that the character of the radical will undergo a change in conformity with this view. For example, the original acetyl radical C_4H_6 of Regnault which was employed to show the relationship between aldehyde, acetic acid and allied compounds (p. 16), was now broken up by Kolbe into the conjunct methyl, which was attached to carbon thus, $(C_2H_3)^-C_2$. The radical contained two pairs of carbon equivalents, and different functions were ascribed to each. It was the pair lying outside the radical which was supposed to afford the point of attachment for oxygen and chlorine. Some of Kolbe's formulae appear as follows:³



¹ *Quart. J. Chem. Soc.*, 1850, 2, 157; *Alcmbic Club Reprints*, No. 15; *Annalen*, 1849, 69, 257.

² It is a curious fact that the formulae of both hydrocarbons (in Kolbe's notation they stood for C_2H_6 , C_8H_{18}) are given correctly, though transposed into the modern form they would stand for CH_4 and C_4H_{10} . The correspondence is accidental, and arises on the one hand from the use of the double molecular formula for the acid, and on the other from the fact that the radicals unite in pairs and form substances having molecular weights double of those recognized by the author of the memoir.

³ See footnote 2 on previous page.

$(C_2H_3)C_2Cl_3$ Dichloro-hydrochloric ether (trichloroethane)

$(C_4H_3)O \cdot (C_2Cl_3)C_2O_3$ Trichloroacetic ether

$(C_2H_3)C_2 \left\{ \begin{array}{l} O_2 \\ NH_2 \end{array} \right.$ Acetamide

$(C_2H_3)C_2N$ Methyl cyanide

In this way methyl was recognized as an integral part not only of acetic acid, but of marsh gas $(C_2H_3)H$, which it yielded on distillation with lime, and of cacodyl oxide, written $(C_2H_3)_2As_2O$, which it formed on heating the potassium salt with arsenious oxide. It explained, moreover, why the last equivalent of hydrogen in chloral $HO, (C_2Cl_3)C_2O$ was not replaced by chlorine. The same system was applied to other acids, benzoic acid and its derivatives being represented by oxalic acid conjugated with the radical phenyl $C_{12}H_5$:

$HO, (C_{12}H_5)C_2O_3$ Benzoic acid

$HO, (C_{12} \left\{ \begin{array}{l} H_4 \\ NO_4 \end{array} \right\} C_2O_3$ Nitrobenzoic acid

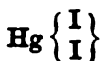
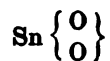
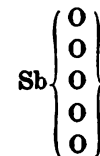
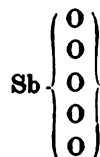
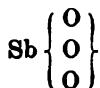
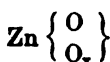
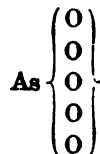
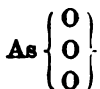
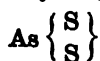
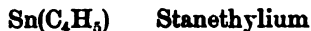
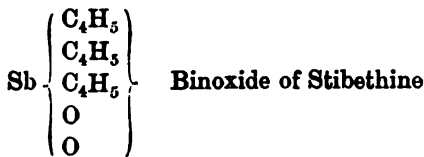
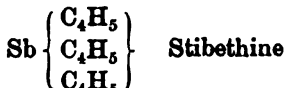
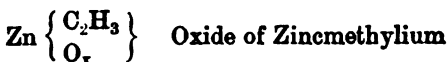
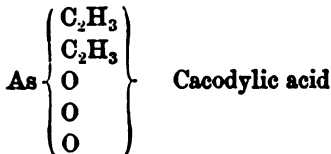
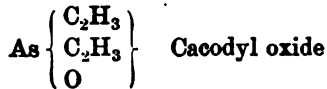
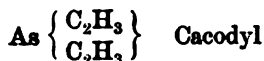
$HO, (C_{12} \left\{ \begin{array}{l} H_4 \\ NH_2 \end{array} \right\} C_2O_3$ Amidobenzoic acid

For the same reason that marsh gas became the hydride of methyl, benzene appeared as the hydride of phenyl $(C_{12}H_5)H$, and phenol as its oxyhydrate $HO \cdot (C_{12}H_5)O$.¹ In this way Kolbe sought to rehabilitate the compound radical:

The constitution attached to cacodyl oxide was later extended to cacodyl and the organo-metallic compounds generally in which the radicals appeared as the conjuncts of the metals. Kolbe was, indeed, the first to interpret correctly the constitution of cacodyl to the extent of regarding it as arsenide of methyl $(C_2H_3)_2As$.

Frankland dissented from this view. It was generally admitted that the saturation capacity of a substance was retained in a conjugated compound. Oxalic acid has the same saturation capacity in the free state as when conjugated with the radical methyl C_2H_3 in acetic acid. This was not the case with the metal in the organo-metallic compounds. Cacodyl in cacodylic acid, which is the highest oxidation product, is only united to three atoms of oxygen instead of five as in arsenic acid, to two in antimony ethyl and to only one in tin ethyl. He preferred to represent these compounds as substitution products of the metallic oxides:

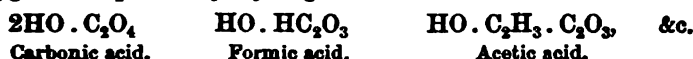
¹ *Annalen*, 1850, 76, 1.

Inorganic types.*Organo-metallic derivatives.*

It was in this memoir¹ that Frankland drew attention to the regularity subsisting between the number of the different kinds of atoms which are found in combination with the same element. This was the first announcement of the doctrine of valency or atomicity, as it was then called, which will be referred to presently (p. 50).

¹ *Phil. Trans.*, 1852, 142, 417.

Kolbe's Views on Constitution. This relation of the organo-metallic compounds to the oxides of the metals, which Frankland first pointed out, suggested to Kolbe a further modification of his theory of conjugated compounds.¹ As cacodylic acid $\text{HO}(\text{C}_2\text{H}_3)_2\text{AsO}_3$ may be derived from arsenic acid $3\text{HO}, \text{AsO}_3$ by replacing two atoms of oxygen by two methyl radicals, so carbonic acid may be regarded as the mother substance of the organic acids in which part of the oxygen is replaced by hydrogen or radicals:

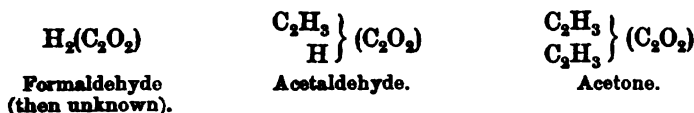


This was a counter-stroke delivered by Kolbe at the artificial inorganic types, as he regarded them, of Gerhardt's new theory which had just appeared (see p. 44). Carbonic acid, the raw material of vegetable synthesis, was on the contrary a natural type from which, as by the vital process, complex derivatives may be obtained.

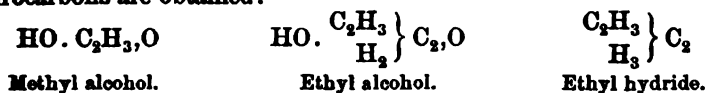
In order to explain the difference of basicity between carbonic acid and the fatty acids, the group C_2O_4 in carbonic acid was split into two $(\text{C}_2\text{O}_3)_2$, and the basicity was made to depend on the number of *extra-radical* oxygen atoms. The above formulae became



Carbonic acid with its two extra radical oxygen atoms is dibasic, whereas formic and acetic acids, with only one, are monobasic. By replacing the last extra-radical oxygen by hydrogen or a radical the neutral aldehydes and ketones result:



If in these more oxygen is substituted, the alcohols and finally the hydrocarbons are obtained:



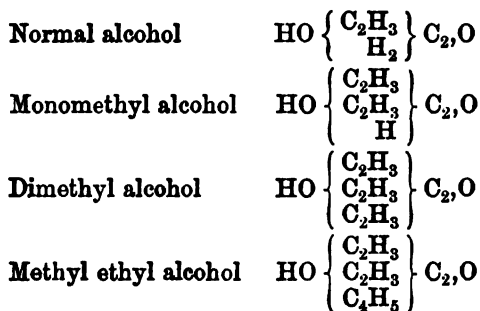
The curious part played by the molecules of water, which sometimes appear upon the scene and again vanish, is due to the insignificant rôle assigned to them by Berzelius and his school.

However fantastic Kolbe's formulae may now appear, the system was in so far successful that it enabled him to foretell the existence of many unknown compounds, some of which, though not all, have since been obtained. Thus, formaldehyde was predicted, and

¹ *Annalen*, 1857, 101, 257; 1860, 113, 293; Ostwald's *Klassiker*, No. 92.

² In these and subsequent memoirs Kolbe discarded the barred atoms.

also the secondary and tertiary alcohols. 'For,' says Kolbe, 'suppose that we introduce into the alcohols in place of one or two atoms of hydrogen the same number of methyl, ethyl, &c., atoms in the same manner (as acetone is derived from aldehyde), we shall obtain new alcohol compounds of the following constitution.'



'The monomethyl alcohol will be isomeric, not identical with propyl alcohol, and dimethyl alcohol will be isomeric with butyl alcohol.'

Two years later the first of these predictions was verified by Friedel, who isolated secondary propyl alcohol, and the second by Butlerow in 1864, who prepared tertiary butyl alcohol. They agreed in nearly every particular with the properties foretold by Kolbe.

'These compounds will probably form, with the hydracids, halogen compounds like ethyl chloride, also sulphur compounds and mercaptans, and with sulphuric acid, sulphuric ethers; but those compounds which are combined like the dimethyl alcohols will not be oxidized to aldehydes and acids, like the normal alcohols, as the two free hydrogen atoms, which in the normal alcohols are attacked, are missing. Nor can the monomethyl alcohols which still retain a free hydrogen atom be converted into acids, but by the same process of oxidation which yields aldehydes in the case of normal alcohols will convert the monomethyl alcohols into acetone.'

We must now pick up the thread of the narrative where we dropped it to follow the fortunes of the radical theory.

The standard of volumes adopted by Gerhardt and Laurent for determining molecular weights served its purpose admirably by bringing together compounds which were related to one another, but gave no information about their structure. The doctrine of residues in its original simplicity could not satisfy the aspirations of chemists in face of the powerful testimony which the researches of Frankland and Kolbe, Hofmann and many other chemists, had brought in support of the radical theory.

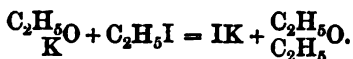
Williamson's Researches on Ether. It was at this critical period in the history of the science that a short and unpretentious memoir appeared, which gave an unexpected turn to the current of chemical thought. This was Williamson's research on etherification, which was first read at the meeting of the British Association at Edinburgh in 1850.¹ It is difficult to embrace in a sentence the far-reaching consequences which followed its publication. In the first place it settled the vexed question of the relation of alcohol to ether; secondly, it introduced a new and important synthetic process; it showed, further, how chemical methods might be employed in determining molecular weights; but above all it reconciled the two contending schools of thought by welding together the radical theory with Dumas' theory of types.

The constitution of alcohol and ether had, as we have seen, received various interpretations. Berzelius regarded them as oxides of different radicals, Liebig formulated ether as the oxide of ethyl and alcohol as its hydrate, Gerhardt in 1844 wrote their formulae C_2H_5O and $C_4H_{10}O$ from the value of their vapour densities, and Laurent in 1846 explained their relation by comparing them to potassium hydrate and potassium oxide, as the hydrate and oxide of ethyl (= Et):²

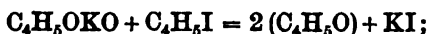


In 1850 Williamson investigated the action of ethyl iodide upon potassium ethylate in the hope of replacing the potassium by ethyl and so forming a new ethylated alcohol.

The experiment gave entirely unexpected results; for, in place of alcohol, he obtained ordinary ether. He recognized the importance of the result, explained by means of it the formation of ether, and demonstrated the correctness of his conclusions in a series of brilliant experiments. Williamson saw at once the application of Laurent's and Gerhardt's views, which he was one of the first to adopt, formulating the reaction thus:



Kolbe strongly opposed this view and represented the reaction as follows:



in which, using the equivalent notation, potassium alcoholate appears as a compound of potash and ether. Substituting methyl iodide for

¹ *Quart. J. Chem. Soc.*, 1852, 4, 229; *Alembic Club Reprints*, No. 16.

² *Chemical Method*, p. 75.

ethyl iodide, methyl ether and ethyl ether should be formed, supposing the latter view to be correct, whilst, according to Williamson's theory, methyl ethyl ether should be formed. It was the second reaction which occurred.

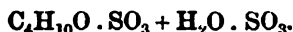
The experiments clearly demonstrated that ether is derived from alcohol by replacing one atom of hydrogen by ethyl, and consequently that it possesses a larger molecule.

It now remained to explain the formation of ether from alcohol and sulphuric acid.

The formation of ether by heating a mixture of alcohol and sulphuric acid is so simple an operation that it seems not a little remarkable that more than two centuries elapsed before the obscurity which enveloped this reaction was finally removed. As the study of this subject and the discussions which rival theories called forth engaged chemists from the very inception of organic chemistry, it will not be entirely out of place to trace the phases of its development. The first method for preparing ether is ascribed to Valerius Cordus in 1540, who called it *oleum vitrioli dulce*, the name being changed to *ether* by Frobenius in 1780. The compound was formed by heating a mixture of alcohol and strong sulphuric acid. Fourcroy and Vauquelin explained the reaction by supposing that alcohol loses a molecule of water. This agreed with the etherin theory and with Liebig's later view. The explanation was, however, open to criticism. Other dehydrating agents, like potash and baryta, effected no change of this kind, and when it was afterwards pointed out that water distilled with the ether, it was difficult to conceive how sulphuric acid could act by reason of its affinity for water if it parted with it in the process. Dabit discovered that the first action of the sulphuric acid on alcohol at the ordinary temperature was the formation of a new acid, which was not precipitated by barium salts. It was termed sulphovinic acid by Sertürner, who studied it more carefully. Then followed the discovery that the contents of the vessel after distilling off the ether could be used for the preparation of fresh quantities of the latter by adding alcohol, an observation upon which Boullay, the father of Dumas' colleague, founded the present continuous process. The first clear experimental evidence as to the nature of this curious and complex reaction is due to Hennel, an English apothecary. He proved that the formation of sulphovinic acid is essential to the process. In the first place he found by distilling equal quantities of sulphuric acid and alcohol that, as the ether distils, the quantity of free sulphuric acid increases, whilst that of the sulphovinic acid decreases. If, on the other hand, the mixture

is first diluted with water, nothing but alcohol passes over, and sulphuric acid remains in the distilling vessel. He further showed that on heating sulphovinic acid, as free as possible from alcohol or water, a certain quantity of ether distils.¹ Berzelius,² in his *Jahresbericht* for 1829, attributes to Hennel the view that ether is formed by the action of alcohol on sulphovinic acid, and since the latter, as Hennel first showed, is a compound of olefiant gas with sulphuric acid, ether must be a compound of olefiant gas with alcohol, a conclusion which bears a striking resemblance to the modern view; but there is nothing in Hennel's original paper which we can find in support of this statement.

Hennel rather suggests that, on heating sulphovinic acid, olefiant gas is separated in a condition which enables it to unite with one proportion of water to form ether and, when diluted, with a larger proportion of water to form alcohol. He subsequently expanded his theory as follows: When sulphuric acid and alcohol are mixed sulphovinic acid and water are formed, the latter diluting a portion of the free sulphuric acid present. On heating the sulphovinic acid, it is the water of this dilute acid which attracts the sulphuric acid of the sulphovinic acid, and enables it to split up into ether and sulphuric acid. It should be remembered that the composition of sulphovinic acid, as determined by Serullas (1829), and later by Liebig and Wöhler (1833), was represented as an acid sulphate of ether, and written



Liebig, as the result of a series of careful experiments, showed that sulphovinic acid does not change below a temperature of 124°, but above that temperature it decomposes into ether, sulphuric acid, and sulphuric anhydride. He attempted to reconcile these facts with Hennel's views in the following manner: the alcohol on falling into the hot sulphuric acid lowers the temperature below 124° at the surface of contact, forming sulphovinic acid and water, which dilutes the sulphuric acid around it. The sulphovinic acid then diffuses into the hotter liquid where it decomposes into ether, which distils, and sulphuric anhydride which combines at once with the water of the dilute acid, regenerating concentrated acid, and is thus capable of uniting with fresh alcohol. The simultaneous distillation of water was accounted for by supposing that the ether vapour carries with it water vapour much in the same way that a high boiling volatile liquid may be distilled in steam. Mitscherlich, however, found that by passing alcohol vapour into the mixture, so that no lowering of

¹ *Phil. Trans.*, 1826, 2, 240.

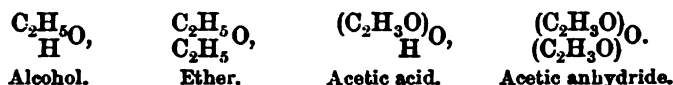
² *Jahresb.*, 1829, 9, 294

temperature occurred, the formation of ether was not interrupted, and both he and Berzelius, and afterwards Graham, explained the peculiar effect of the sulphuric acid as a catalytic or contact phenomenon, by which they understood such a reaction as occurred in the presence of a substance which itself underwent no change, and for which no satisfactory explanation was forthcoming.¹

The composition of ether being now clearly established, Williamson turned the fact to account in order to explain the production of ether from alcohol and sulphuric acid.

The explanation is the one we still adopt. The process occurs in two stages. Sulphovinic acid and water are first produced, and the sulphovinic acid reacting with a fresh quantity of alcohol forms ether and regenerates sulphuric acid. Ether and water distil whilst the sulphuric acid is free to react with fresh alcohol, and repeat the same cycle of changes. Williamson confirmed these views by showing that mixed ethers could be readily obtained by the use of two different alcohols, and prepared in this way a series of compounds containing from three to seven carbon atoms.

In reviewing his results he points out that compounds like alcohol, ether, acetic acid, and its hypothetical anhydride may be regarded as water in which one or two hydrogen atoms are replaced by the radicals ethyl and *othyl* (oxygen ethyl):



This memorable paper, which proved so fruitful in results and provided such a powerful stimulus to future research, concludes with the following words: 'The method here employed, of stating the rational constitution of bodies by comparison with water, seems to me to be susceptible of great extension, and I have no hesitation in saying that its introduction will be of service in simplifying our ideas, by establishing a uniform standard of comparison by which bodies may be judged of.'²

Gerhardt's discovery of the acid anhydrides, in the same year, by heating the acid chlorides with their sodium salts, amply justified Williamson's conclusions.

Gerhardt's New Theory of Types. In the following year, 1853, Gerhardt³ published his new theory of types, already foreshadowed in a memoir by Chancel and himself on *The Constitution of Organic*

¹ *Jahresh.*, 1835, 15, 243.

² *Quart. J. Chem. Soc.*, 1852, 4, 239.

³ *Ann. Chim. Phys.*, 1853, 37, 332.

Compounds, which appeared in the *Revue Scientifique* for 1851. It was a direct outcome of Williamson's memoir on ether, though unacknowledged at the time of its publication.¹

To understand this development we must recall a few facts. In 1849 Wurtz had obtained, by the action of potash on cyanic and cyanuric ethers, bases closely allied in smell and basic characters to ammonia, which he compared to ammonia wherein an atom of hydrogen was replaced by the radicals methyl, ethyl, and amyl.² Although the existence of such compounds had been foretold ten years earlier by Liebig, it was the first successful attempt to introduce radicals into ammonia. This interesting fact is recalled by Liebig himself in a note to Wurtz's paper in the *Annalen*.³

'If one considers the combination NH_3 or amide as a compound radical, which possesses the properties of radicals as opposed to those of acid radicals, it is clear that ammonia is the hydrogen compound of a basic radical, which is similar in composition to hydrocyanic acid, but is the reverse in properties. Hydrogen cyanide is an acid, hydrogen amide has alkaline properties, a difference due to the characters of the radicals which they contain. . . . Now we know that amide is capable of replacing equivalent for equivalent the oxygen of many organic acids, and we find that the new compounds thus produced have altogether lost the nature of acids, being indifferent in their chemical character. . . . If in the oxides of methyl and ethyl, the oxides of two basic radicals, we were able to substitute one equivalent of amide for oxygen, there cannot be the slightest doubt that we should obtain compounds perfectly similar in their behaviour to ammonia. Expressed in a formula a compound $\text{C}_4\text{H}_5 + \text{NH}_2 = \text{E} + \text{Ad}$ must have basic properties.'

The character which Wurtz attached to these compounds was soon afterwards confirmed by Hofmann, who obtained what are known as the primary, secondary, and tertiary bases by the action of the iodides of the alcohol radicals on aniline and ammonia.⁴

The organic phosphorus compounds which Paul Thénard had discovered in 1845 now received an analogous interpretation. In addition to these new classes of compounds, the acid chlorides had been prepared by Cahours⁵ in 1845, and the anilides and other amides by Gerhardt and Chiozza⁶ in 1853.

¹ *Vie de Gerhardt*, p. 412.

² *Compt. rend.*, 1848, 26, 368; 27, 241; 1849, 28, 223, 323; 29, 169, 186, 203; *Annalen*, 1849, 71, 326.

³ *Annalen*, 1849, 71, 347.

⁵ *Compt. rend.*, 1845, 21, 145; 1847, 25, 892.

⁴ *Annalen*, 1850, 73, 91; 1851, 79, 16.

⁶ *Compt. rend.*, 1853, 37, 86.

All these groups of compounds were now referred by Gerhardt to four types. In expounding his theory he says: 'I do not attach to these so-called *rational* formulæ, which give the molecular constitution of chemical compounds, any exaggerated value, because they are in fact only the expression of a partial truth, which in a more or less complete fashion includes a certain number of chemical changes. Such formulæ, however, appear to me to have their use, for they may exert a happy influence on the development of the science, if they are viewed from the same standpoint and accord well together.'

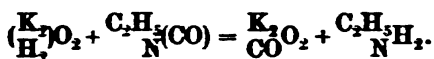
The four types which he proposes are water, H_2O , hydrogen, H_2 , hydrochloric acid, HCl , and ammonia, NH_3 . Each vertical series is derived from the type by replacing the hydrogen by radicals :

$\begin{array}{c} \text{H} \\ \text{H} \end{array} \}$	$\begin{array}{c} \text{H} \\ \text{Cl} \end{array} \}$	$\begin{array}{c} \text{H} \\ \text{H} \end{array} \} \text{O}$	$\begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \end{array} \} \text{N}$
Type.	Type.	Type.	Type.
$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{H} \end{array} \}$	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{Cl} \end{array} \}$	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{H} \end{array} \} \text{O}$	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{H} \\ \text{H} \end{array} \} \text{N}$
Ethyl hydride.	Ethyl chloride.	Ethyl alcohol.	Ethylamine.
$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{array} \}$	$\begin{array}{c} \text{C}_2\text{H}_5\text{O} \\ \text{Cl} \end{array} \}$	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{array} \} \text{O}$	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \\ \text{H} \end{array} \} \text{N}$
Diethyl.	Acetyl chloride.	Ethyl ether.	Diethylamine.
$\begin{array}{c} \text{C}_2\text{H}_3\text{O} \\ \text{H} \end{array} \}$	$\begin{array}{c} \text{C}_7\text{H}_5\text{O} \\ \text{Cl} \end{array} \}$	$\begin{array}{c} \text{C}_2\text{H}_3\text{O} \\ \text{H} \end{array} \} \text{O}$	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{array} \} \text{N}$
Aldehyde.	Benzoyl chloride.	Acetic acid.	Triethylamine.
$\begin{array}{c} \text{C}_2\text{H}_3\text{O} \\ \text{CH}_3 \end{array} \}$	$\begin{array}{c} \text{CN} \\ \text{Cl} \end{array} \}$	$\begin{array}{c} \text{C}_2\text{H}_3\text{O} \\ \text{C}_2\text{H}_3\text{O} \end{array} \} \text{O}$	$\begin{array}{c} \text{C}_2\text{H}_3\text{O} \\ \text{H} \\ \text{H} \end{array} \} \text{N}$
Acetone.	Cyanogen chloride.	Acetic anhydride.	Acetamide.

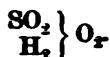
They were in a sense mechanical rather than chemical types, for the members of one type were connected together more in outward form than in properties; but the typical formulæ served admirably to express double decompositions, to indicate the relation which the function of an element bears to its position in the type, and finally, to explain cases of isomerism.

Inorganic compounds were also constructed on the system of types, nitric acid being represented by Williamson as $\begin{array}{c} \text{NO}_2 \\ \text{H} \end{array} \} \text{O}$, to which Gerhardt added Deville's nitric anhydride $\begin{array}{c} \text{NO}_2 \\ \text{NO}_2 \end{array} \} \text{O}$.

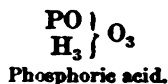
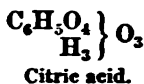
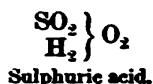
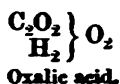
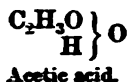
Condensed Types. In developing his views on the constitution of the ethers, Williamson had already introduced the idea of the condensed water type. He pointed out that it may be usefully employed in formulating the action of potash on the organic ethers.¹



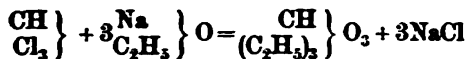
In this equation the two atoms of hydrogen in the double molecule of potash are replaced by the group CO. Williamson recognized in this the existence of what we now term a multivalent radical, which was then called by analogy with the polybasic acids, a *polybasic radical*. The group CO was therefore dibasic, or, according to Gerhardt, diatomic. The group SO₂ was regarded in the same light, the formula for sulphuric acid being derived from a condensed water type of two molecules and written



Odling extended the idea to other inorganic and organic acids,² and to the metals themselves:



Wurtz's Researches on Glycol. In 1854 Williamson and Kay obtained orthoformic ether by the action of sodium ethylate on chloroform:³



This was the first example of a tribasic hydrocarbon radical. About the same time Berthelot was engaged in the investigation of glycerine, and found that it unites in three distinct proportions with acids, forming acetins, stearins, and chlorhydrins, &c. He concluded

¹ *The Chemical Gazette*, 1851, 9, 334; *Alcumbic Club Reprints*, No. 16, 46.

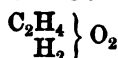
² *Quart. J. Chem. Soc.*, 7, 1.

³ *Proc. Roy. Soc.*, 1854, 7, 135.

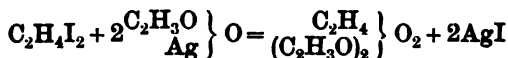
that glycerine bore the same relation to phosphoric acid that alcohol does to nitric acid :



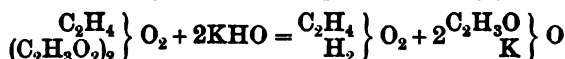
Wurtz quickly perceived that a compound intermediate between alcohol and glycerine should exist, derived from a double water type, and containing a dibasic radical. Before long he had supplied the necessary link by the discovery of glycol :¹



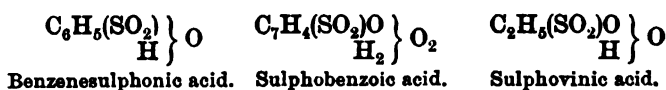
He prepared the compound from ethylene iodide and silver acetate, which, on heating together, yield ethylene acetate and silver iodide. Using the typical formulae, the equation appears thus :



Ethylene acetate on hydrolysis with potash forms glycol :



Mixed Types. The use of condensed types was shortly followed by the introduction of Kekulé's *mixed types*,² which he set forth in a paper *On the so-called Conjugated Compounds and the Theory of Polyatomic Radicals*. Kekulé's object was to explain the constitution of Gerhardt's new conjugated radicals, that is, the old conjugated compounds which, in their new typical garb, played the part of substituted radicals. Benzenesulphonic acid, sulphobenzoic acid, and sulphovinic acid were written



Benzenesulphonic acid may be represented, according to Kekulé,³ as derived from the two types of hydrogen and water,



¹ *Ann. Chim. Phys.*, 1859 (3), 55, 400.

² *Annalen*, 1857, 104, 129.

³ Following a suggestion of Williamson, the symbols for oxygen, carbon, sulphur were barred in Kekulé's formulae to indicate that the combining weights were double those of the equivalent notation.

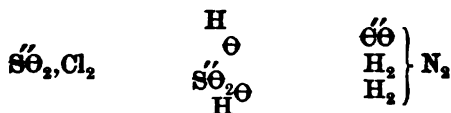
Oxamic acid may, in the same way, be referred to a mixed water and ammonia type :



Kekulé's Theory of Atomicity. Kekulé at once saw, as Williamson had previously done (p. 47), that such a fusion of types to a condensed or mixed type can only occur where a polybasic or polyatomic radical is present in the place of two or three atoms of hydrogen. Using the dashes of Odling to indicate atomicity and the double atoms, which Williamson had revived to distinguish Gerhardt's atomic weights ($\text{C}=12$, $\text{O}=16$) from Gmelin's equivalents ($\text{C}=6$, $\text{O}=8$), Kekulé defines the radicals as follows :

'A *monatomic* radical can, therefore, never hold together two molecules of the types.'

'A *diatomic* radical can unite two molecules of the types,' e. g.

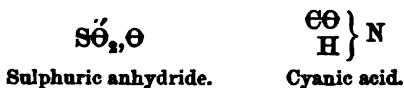


Thionyl chloride.

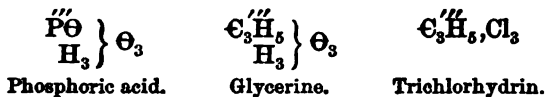
Sulphuric acid.

Urea.

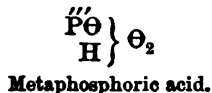
or, can replace two hydrogen atoms of the type, e. g.



'A *triatomic* radical can unite in the same way three molecules of the types,' e. g.



or it can also replace three atoms of hydrogen in two molecules of water, e. g.



Perhaps the most important part of this remarkable and suggestive memoir is the reference to the basicity, i. e. valency of the individual elements.

Growth of the Theory of Valency. As the whole foundation of modern structural chemistry may be said to rest upon the theory of valency, it is necessary to trace carefully the line of thought which culminated in its development.

It is just possible that had no previous literature existed on the subject, this property of the elements would have disclosed itself to Kekulé's penetrating intellect. It is none the less true that the merit of having been the first to offer a clear exposition of the subject belongs to Frankland.

In studying the organo-metallic compounds, to which reference has been made (p. 37), Frankland was struck with the fact that there appears to be a definite saturation capacity for the metals, and that the number of radicals present affects the number of inorganic elements which attach themselves to the metal in a symmetrical fashion. It was this fact which led him to oppose Kolbe's view that the radicals are conjugated with the metal. At the close of this paper¹ Frankland expressed himself as follows: 'When the formulæ of inorganic chemical compounds are considered, even a superficial observer is struck with the general symmetry of their construction; the compounds of nitrogen, phosphorus, antimony, and arsenic especially exhibit the tendency of these elements to form compounds containing three or five equivalents of other elements, and it is in these proportions that their affinities are best satisfied; thus in the ternary group we have NO_3 , NH_3 , NI_3 , NS_3 , PO_3 , PH_3 , PCl_3 , SbO_3 , SbH_3 , SbCl_3 , AsO_3 , AsH_3 , AsCl_3 , &c.; and in the five-atom group NO_5 , NH_4O , NH_4I , PO_5 , PH_4I , &c. Without offering any hypothesis regarding the cause of this symmetrical grouping of atoms, it is sufficiently evident, from the examples just given, that such a tendency or law prevails, and that *no matter what the character of the uniting atoms may be, the combining power of the attracting element, if I may be allowed the term, is always satisfied by the same number of these atoms.*'

Two years later, in his first publication of theoretical importance, *Note on a New Series of Organic Acids containing Sulphur*,² Kekulé refers to the basicity of the elements. Various organic compounds of the water type such as alcohol, ether, acetic acid, and acetic anhydride were heated with the sulphides of phosphorus and the typical oxygen replaced by sulphur. He shows that the new typical formulæ of Gerhardt are well adapted for expressing these changes. If, according to the equivalent notation, phosphorus chloride breaks

¹ *Phil. Trans.*, 1852, 417.

² *Annalen*, 1854, 90, 309.

up alcohol into $C_4H_5Cl + HCl$, why should not phosphorus sulphide produce two compounds $C_4H_5S + HS$ instead of their remaining united as mercaptan? With Gerhardt's notation the change is manifest, $\left. \begin{smallmatrix} C_2H_5 \\ H \end{smallmatrix} \right\} O$ becomes $\left. \begin{smallmatrix} C_2H_5 \\ H \end{smallmatrix} \right\} S$, but with phosphorus chloride

the alcohol divides up thus, $\frac{C_2H_5Cl}{H Cl}$. He writes: 'It is not merely

a difference of notation, but it is an actual fact that one atom of water contains two atoms of hydrogen and only one atom of oxygen; and that for one indivisible atom of oxygen the equivalent of chlorine is divisible by two; whereas sulphur, like oxygen, is dibasic, one atom being equivalent to two of chlorine.'

In the memoir already referred to (p. 48), *On the so-called Conjugated Compounds and the Theory of Polyatomic Radicals*,¹ Kekulé's views on atomicity take a clearer and more definite shape. He says: 'The molecules of chemical compounds are formed by the union of atoms. The number of atoms of other elements which are attached to one atom of an element, or (if in the case of compound bodies one prefers not to extend the idea to elements) of a radical, is dependent on the basicity or affinity of the constituents.'

'The elements fall into three main groups:

'(1) Monobasic or monatomic, e.g. H, Cl, Br, K; (2) dibasic or diatomic, e.g. O, S; (3) tribasic or triatomic, e.g. N, P, As. From these are derived the chief types, HH, OH₂, NH₃, and the secondary types, HCl, SH₂, PH₃.' In a footnote on p. 188 he adds that carbon is tetrabasic or tetraatomic.

After this defence of Gerhardt's formulæ and clear exposition of atomic structure, it is curious to find Kekulé reverting to the equivalent notation in his very next memoir on the constitution of fulminating mercury; but such is the despotic power of long established custom.

In discussing the constitution of fulminating mercury, Kekulé² pointed out its analogy with a series of compounds which might be considered as belonging to the same type as marsh gas, using the word in Dumas' sense of one compound being related to another by substitution. He succeeded, in fact, in liberating the cyanogen as cyanogen chloride by chlorination, and converting fulminating mercury into chloropierin.

Methyl chloride, chloroform, chloropierin, and acetonitrile were

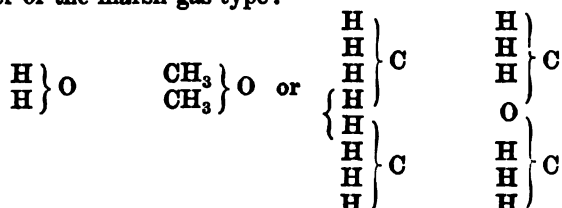
¹ *Annalen*, 1857, 104, 138.

² *Annalen*, 1857, 101, 200.

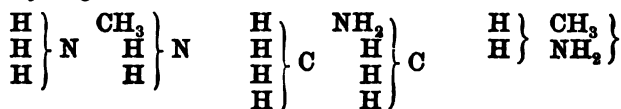
grouped with marsh gas, and written in the equivalent notation thus:

C ₂	H	H	H	H	Marsh gas
C ₂	H	H	H	Cl	Methyl chloride
C ₂	H	Cl	Cl	Cl	Chloroform
C ₂	(NO ₄)	Cl	Cl	Cl	Chloropicrin
C ₂	H	H	H	(C ₂ N)	Acetonitrile
C ₂	(NO ₄)	Hg	Hg	(C ₂ N)	Fulminating mercury

Thus Kekulé introduced a new type, that of marsh gas, and with its introduction the fixity of Gerhardt's types was dissolved; for it now became evident that the grouping of the elements depended, not on the nature of the type, but upon that of the elements themselves. As typical formulæ were not intended to represent the position of the atoms, it became a matter of choice to which type a compound belonged. Thus, methyl ether may be equally well derived from the water or the marsh gas type:



Methylamine in the same way may be referred to ammonia, marsh gas, or hydrogen:



Quadrivalence of Carbon. Early in 1858 Kekulé's celebrated paper appeared in Liebig's *Annalen* on *The Constitution and Metamorphoses of Chemical Compounds, and on the Chemical Nature of Carbon*, in which are embodied his views on the valency of carbon and the linking of carbon atoms.¹ Shortly afterwards an equally remarkable memoir on the same subject by A. S. Couper² was published independently in the *Annales* under the title of *A new Chemical Theory*.

Kekulé's Theory. Kekulé has told, in a very graphic way, how these new ideas arose. It was during his stay in London.

'One fine summer evening I was returning by the last omnibus

¹ *Annalen*, 1858, 106, 129; Ostwald's *Klassiker*, No. 145.

² *Ann. Chim. Phys.*, 1858 (3), 53, 469.

"outside" as usual, through the deserted streets of the metropolis, which are at other times so full of life. I fell into a reverie, and lo! the atoms were gambolling before my eyes! Whenever, hitherto, these diminutive beings had appeared to me they had always been in motion; but up to that time I had never been able to discern the nature of their motion. Now, however, I saw how, frequently, two smaller atoms united to form a pair; how a larger one embraced two smaller ones; how still larger ones kept hold of three or even four of the smaller; whilst the whole kept whirling in a giddy dance. I saw how the larger ones formed a chain, dragging the smaller ones after them, but only at the ends of the chain. . . . This was the origin of the *Strukturtheorie*.¹

'If we consider,' writes Kekulé in his memoir, 'the simplest compounds of carbon, CH_4 , CH_3Cl , CCl_4 , CHCl_3 , COCl_2 , CO_2 , CS_2 , CHN , it is very striking that the amount of carbon which chemists recognize as the atom, that is, the smallest part, always unites with four atoms of a monatomic or two of a diatomic element, that generally the sum of the chemical units which are bound to an atom of carbon is equal to four. This leads to the view that carbon is tetratomic.'

'For substances which contain several atoms of carbon, one must suppose that a portion of the atoms at least is held by the attraction of the carbon, and that the carbon atoms themselves are united to one another, whereby naturally a part of the attraction of the one is neutralized by an equal attraction on the part of the other.'

'The simplest and consequently most probable case of such a union of two carbon atoms is that one unit of affinity of one carbon atom is bound to one of the other. Of these 2×4 units of affinity of the two carbon atoms, two will be used to unite the two carbon atoms, and six will remain over to attach the other elements. In other words the group C_2 is hexatomic. . . .'

'If more than two carbon atoms unite in the same way, the basicity of the carbon group will be increased by two units for each additional carbon atom. Thus the number of hydrogen atoms which may be combined with n carbon atoms is expressed by

$$n(4 - 2) + 2 = 2n + 2.$$

' . . . Up to this point we have assumed that all the atoms attaching themselves to carbon are held by the affinity of the carbon. It is equally conceivable, however, that in the case of polyatomic elements (O, N, &c.) only a part of the affinity—for example, only one of the

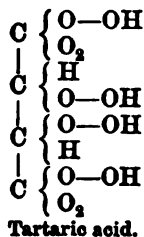
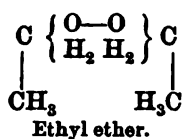
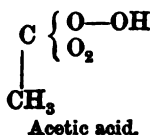
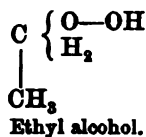
¹ The Kekulé Memorial Lecture, by F. R. Japp, *Trans. Chem. Soc.*, 1898, 73, 97.

two units of affinity of the oxygen, or only one of the three units of the nitrogen—is attached to carbon; so that one of the two units of affinity of the oxygen and two of the three units of affinity of the nitrogen remain over and may be united with other elements. These other elements are therefore only in indirect union with the carbon, a fact which is indicated by the typical mode of writing the formulae.

Kekulé does not recognize only this one kind of attachment of the carbons. He points out that another kind of combination may occur involving a closer union of the carbon atoms, an idea which was expanded seven years later (1865) in his theory of the benzene ring.

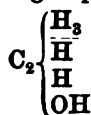
Couper's Theory. Couper arrived at similar conclusions from a different starting-point. His paper, which is characterized by remarkable perspicuity and breadth of view, has perhaps scarcely received the full recognition which it merits. Couper begins by rejecting the type theory of Gerhardt as artificial and unphilosophical, and lays stress on the fact that the properties of compounds must in the end depend on the nature of their atoms. Gerhardt's system is like referring a language to certain types of words, from which all others are formed, instead of to the individual letters. The atoms, he considers, are held together by virtue of two properties, *elective affinity* or chemical affinity and *degree of affinity*, which corresponds exactly to our word valency.

In regard to carbon (1) it unites with an even number of hydrogen atoms, and (2) it unites with itself. The maximum number of atoms with which it can combine is four. The following are some of the formulae proposed by Couper which, apart from the presence of the double atom of oxygen, bear a complete resemblance to those in modern use ($C = 12$; $O = 8$):



The two papers by Kekulé and Couper are the foundations upon which the modern structural formulae of organic compounds rest. It must not be supposed that the typical formulae were at once discarded in favour of the modern notation. On the contrary, the typical notation was in general use for many years after the above memoirs had appeared, and was even retained in Kekulé's textbook of organic chemistry which was published as late as 1866. It is evident, from the facts recorded in the next chapter having reference to the basicity of lactic acid, that the true significance of Kekulé's and Couper's views had not then (1863) taken root.

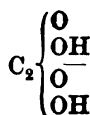
Modern Structural Formulae. It is in fact difficult to assign any particular date to the introduction of the modern structural notation. Its adoption was the result of a gradual and almost imperceptible development. Frankland made a distinct advance by deriving his compounds from the marsh gas or its condensed type, and breaking up the rest of the molecule attached to the typical carbon atoms into tervalent groups thus :



Alcohol.



Acetic acid.



Oxalic acid.

Although there is evidence that the principle of carbon linkages, like that suggested by Couper, was fully recognized before its actual adoption,¹ it was not until 1866 that the first appearance of the modern system of notation occurs in two papers by Erlenmeyer,² followed in 1867 by a clear exposition of the subject by Frankland.³

The necessity for the replacement of rational by structural formulae became more and more emphasized with the growth of the subject, and especially with the extension of the views on isomerism which demanded a more delicate and perfect language for its expression.

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¹ Kekulé's *Lehrbuch der organ. Chem.*, vol. i, pp. 164 and 174.

² *Annalen*, 1866, 137, 351; 139, 211.

³ *Annalen*, 1867, 142, 1.

CHAPTER II

ISOMERISM AND STEREOISOMERISM

Historical. It is scarcely a matter of surprise that, in the early history of the science, inorganic chemistry, the older and more highly developed branch, should have bequeathed to organic chemistry its formulas and doctrines. Every inorganic substance had, or was assumed to have, its own distinctive composition, and the principle was tacitly applied to organic compounds.

That two substances might have the same composition and yet possess different properties was first clearly recognized by Faraday. It appears that in 1820 Dalton obtained (by the distillation of certain fatty oils) a hydrocarbon which combined with chlorine like olefiant gas, and he drew the shrewd conclusion that 'most probably the atom of the new gas consists of two of olefiant gas'. This suggestion was afterwards confirmed by Faraday, who in 1825 undertook an investigation into the nature of the oil gas, which was being manufactured by the Portable Gas Company compressed into metal vessels and distributed among consumers. This compressed gas contained a considerable quantity of a liquid of low boiling-point, from which Faraday isolated a hydrocarbon which had the same composition as olefiant gas but twice its density. It was on the same memorable occasion that benzene was discovered. Of the former hydrocarbon Faraday wrote: 'In reference to the existence of bodies composed of the same elements and in the same proportion, but differing in their qualities, it may be observed that now we are taught to look for them they will probably multiply.'

He pointed out the existence of a similar example in the case of the fulminates of Liebig and the cyanates and cyanurates of Wöhler.

In 1828 Wöhler obtained urea (p. 9) which possessed the same composition as ammonium cyanate but different properties. The existence of substances of this character aroused a lively interest; for Berzelius, in his *Jahresbericht* for 1829, after describing the artificial preparation of urea, proceeds: 'This fact opens the door to clearer views and indicates that the number of simple atoms may be distributed in the compound in various ways, and thereby give rise

to compounds with different properties, as we have already begun to discover in other cases.'

Two years later Berzelius, in studying an acid which had been found in the mother liquors from the manufacture of tartaric acid by Kastner, a manufacturer of Thann,¹ showed that it possessed the same composition as tartaric acid, but different properties, and named it racemic acid (*Traubensäure*). It is an interesting fact that, although Berzelius at first accepted the principle of isomerism with the greatest reserve, he should himself have been the discoverer of that notable example which was in later years to give rise to the modern conception of stereoisomerism, or the different arrangement of atoms in space.

In reference to his discovery of racemic acid in the *Jahresbericht* for 1831, Berzelius writes: 'The absolute identity in composition of two compounds possessing different properties has now been positively established by the analysis of racemic acid, an acid of organic origin. This acid has the same composition, contains the same elements in the same atomic proportion, and possesses the same saturation capacity as tartaric acid.' He proceeds to explain it by a different arrangement of the atoms, and points out that Mitscherlich's discovery of isomorphism must undergo a further extension; for as isomorphous bodies consist of different atoms similarly arranged in the crystalline state, so the same atoms may be grouped in such a way as to produce different crystalline substances, which is the case with tartaric and racemic acid. In order to distinguish these substances he proposes to use the word 'isomeric', from *ισομερής*, composed of equal parts. In the following year² he added the terms *polymerism* (*πολύς*, several) to indicate compounds possessing the same proportion but a different total number of atoms, and *metamerism* (*μετά*, used in the sense of metamorphosis) to denote isomeric compounds so nearly related that they can undergo reciprocal conversion like cyanic and cyanuric acid.

Thus the principle of isomerism became an established fact in organic chemistry, and, as Faraday had foretold, examples soon began to multiply.

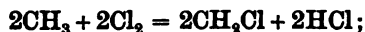
Isomerism of the Paraffins. One case of isomerism long and strenuously upheld was opposed to the new system laid down by

¹ Racemic acid had been previously examined by Gay-Lussac without definite results. Kastner never succeeded in reproducing this acid. The story of Pasteur's pilgrimage in 1852 in the search for the source of the acid is one of the veritable romances of chemistry: *Vie de Pasteur*, p. 70, by Vallery-Radot.

² *Jahresb.*, 1832, 12, 68.

Kekulé, and was eventually shown to rest on insecure experimental data. This was the two series of hydrocarbons known as the free alcohol radicals and their hydrides.

Reference has already been made to the experiments instituted by Frankland and Kolbe to isolate the radicals (p. 84). It was there stated that by the action, first of potassium on the cyanide, and later of zinc on the iodide of the radical, the radical itself was set free. From methyl iodide, methyl (CH_3) was supposed to be liberated, and, from ethyl iodide, the radical ethyl (C_2H_5). Subsequently by the action of zinc and water on ethyl iodide Frankland obtained a hydrocarbon, which he called ethyl hydride $\text{C}_2\text{H}_5 \cdot \text{H}$. The formulae given to the hydrocarbon radicals, methyl (CH_3), ethyl (C_2H_5), &c., were contrary to the law of even numbers of Gerhardt and Laurent, who doubled them (p. 81). Many other chemists, notably Hofmann, Brodie, and Kopp, took the same view, pointing out that the physical properties—vapour density, boiling-point, and molecular volume—demanded the double formula. This was subsequently conceded, and methyl appeared as $(\text{CH}_3)_2$, ethyl as $(\text{C}_2\text{H}_5)_2$. But the question was then raised as to the identity of methyl with ethyl hydride. Frankland maintained that they were isomeric, an opinion which he based on the behaviour of the two hydrocarbons towards chlorine. He alleged that by the action of two volumes of chlorine on one volume of the hydrocarbons a gas was obtained from methyl without change of volume, according to the equation



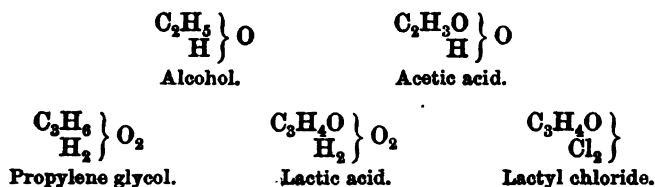
but in the case of ethyl hydride two volumes of hydrochloric acid were formed, and at the same time a liquid was produced which probably had the formula $\text{C}_2\text{H}_4\text{Cl}_2$. These statements were afterwards contested by Schorlemmer¹ (1867), who by a careful repetition of Frankland's experiments and by his own original investigations demonstrated the incorrectness of Frankland's results. He showed conclusively that both hydrocarbons yield the same products, ethyl chloride and ethyl alcohol, and at the same time established the identity of other chlorides and alcohols, obtained from the natural paraffins, with those prepared from the synthetic hydrocarbons, which he obtained by the action of sodium on the iodides of the radicals.

Isomerism of the Lactic Acids. A special interest centres round the constitution of lactic acid which represents an early example of isomerism. It was discovered in 1780 by Scheele in

¹ *Proc. Roy. Soc.*, 1864, 13, 225 et seq.; *Trans. Chem. Soc.*, 1864, 17, 262.

sour milk. In 1807 Berzelius isolated a lactic acid from the juice of flesh, without however having a clear conception of its nature.¹ It was not until Liebig and Mitscherlich reinvestigated the subject in 1832 that the individuality of the sour milk acid was definitely established. In 1847 Liebig² further drew attention to the character of the salts, notably the zinc and calcium salts of the acid from the juice of flesh, which he considered to be identical with the sour milk acid, until Engelhardt,³ in the following year, pointed out the difference between them.

The theme was by no means exhausted, for between the years 1858 and 1860 the basicity of lactic acid became the object of a lively controversy. Although Liebig had determined the formula to be $C_3H_5O_3$, Gerhardt regarded the acid as dibasic and the formula was doubled. Strecker's synthesis of alanine from aldehyde and the conversion of the former into lactic acid led to the re-adoption of the older formula. The correctness of this view was subsequently confirmed by Wurtz, who prepared the acid by the oxidation of propylene glycol.⁴ Kolbe and Wurtz were, however, divided on the question of its basicity. Wurtz held it to be dibasic by reason of its connection with propyl glycol (to which it stands in the same relation as alcohol to acetic acid), a view which he expressed by the following typical formulae:



With phosphorus chloride it yields lactyl chloride. Both reactions indicated the presence of two *typical* hydrogen atoms. Kolbe, on the other hand, regarded it as monobasic and called it oxypropionic acid, which expressed the same relation to propionic acid that glycollic bears to acetic or oxybenzoic to benzoic acid. In support of his view he pointed out that glycocoll, alanine, and amidobenzoic acid are converted in the same manner by nitrous acid into the respective oxyacids. Moreover, the glycols, he alleged, were not alcohols, but oxyhydrates, as they neither yielded nor, according to his formulae,

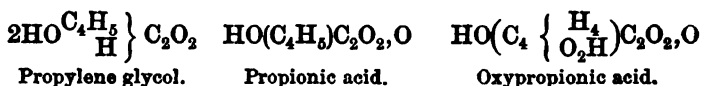
¹ *Treatise*, vol. ix, 573; *Jahresb.*, 1823, 2, 73; *Annalen*, 1832, 1, 1.

² *Annalen*, 1847, 62, 326.

³ *Annalen*, 1848, 65, 359.

⁴ *Compt. rend.*, 1858, 46, 1223; *Annalen*, 1858, 107, 192.

could yield aldehydes on oxidation.¹ He wrote the formulae as follows:



Lactyl chloride was explained as chloropropionyl chloride, for the two chlorine atoms possess different functions, one only being acted upon by water, forming chloropropionic acid, or by alcohol, giving chloropropionic ether.²

Fresh proofs were now brought forward by Wurtz in favour of the dibasic nature of the acid. Brünig had obtained dibasic tin salts of the acid, and Wurtz had prepared, by the action of sodium ethylate on chloropropionic ether, the diethyl ether of lactic acid.

The reduction of lactic acid to propionic, which had recently been accomplished by Ulrich, and the fact that Wurtz's diethyl ether only lost one alcohol radical on boiling with caustic soda, were adduced by Kolbe in support of his view.³ So the discussion continued, new facts being advanced by both disputants.⁴ Wurtz had meantime introduced the distinction between atomicity and basicity: whereas basicity is determined by the number of hydrogen atoms replaceable by a metal, the atomicity is conditioned by the valency of the radical. Although glycol contains two typical hydrogen atoms neither is basic, whilst in glycollic acid one of the two is basic and in oxalic acid, both.

But the distinction found no expression in Wurtz's typical formula, and it was left to Wislicenus⁵ to show that the two views might be very simply reconciled by translating Kolbe's formula into the *typical* notation, which meant the subdivision of the type into smaller types. Wislicenus' formulae for propionic and lactic acid appeared as follows:



The inner water type represents alcoholic, the outer one, acid properties; or, as Wislicenus expressed it, the diatomic and negative

¹ On this one point Kolbe was, of course, in error, for he did not admit Debus' glyoxal to be the aldehyde of glycol.

² *Annalen*, 1859, 108, 257.

⁴ *Annalen*, 1861, 119, 369.

³ *Annalen*, 1860, 113, 228.

⁵ *Annalen*, 1863, 125, 41.

radical, carbonyl, is half neutralized by the positive alcohol radical, whilst the second half retains its monobasic acid character. These relations were more clearly emphasized when Kekulé's graphic formulae came into general use, which followed shortly after the publication of his textbook.¹

The structure of the second lactic acid from flesh, called by Heintz *paralactic* acid and by Strecker *sarcolactic* acid, was still unexplained, as well as the connection subsisting between these two and a new isomeric acid which shortly appeared on the scene.

In 1863 Wislicenus² effected the synthesis of lactic acid by the action of potassium cyanide on ethylene chlorhydrin, which yielded the cyanhydrin, and this, on hydrolysis, formed the new or ethylene lactic acid.³ At first he pronounced the product to be identical with Liebig's paralactic acid; but, on reinvestigating the matter, he recognized Liebig's acid as a mixture of an optically active acid with a small quantity of his own acid.⁴ There were therefore three acids. A fourth isomeric acid was stated by Beilstein to be formed by the action of silver oxide and water on β -iodopropionic acid, and named by him hydraacrylic acid, from its ready decomposition into acrylic acid by heat; but its identity with ethylene lactic acid was subsequently established by Wislicenus.⁵

The existence of more than two structurally different acids at the time Wislicenus published his final paper on the subject in 1878 could not be explained by any current hypothesis, and in reviewing his results he draws attention to the necessity for extending the conception of atomic grouping. 'If it is once granted that molecules can be structurally identical and yet possess dissimilar properties it can only be explained on the ground that the difference is due to a different arrangement of their atoms in space.'⁶

Isomerism of the Tartaric Acids. Many years before the appearance of the first memoir of the German chemist a partial solution of a similar problem had been offered by the French chemist, Louis Pasteur. Pasteur did not range far into the field of chemistry, but during the few years (1848-54) that he laboured at the subject he struck so rich a vein of scientific wealth that, after the lapse of half a century, it still remains unexhausted. The fascinating story of his discovery is told in two lectures on 'Molecular Asymmetry' delivered before the Chemical Society of Paris in 1860.⁷

¹ *Lehrbuch der organischen Chemie* (1866). 2.

² *Annalen*, 1863, 128, 1.

³ *Ber.*, 1869, 2, 550.

⁴ *Annalen*, 1873, 187, 343.

⁵ *Annalen*, 1868, 128, 1.

⁶ *Ber.*, 1870, 3, 809.

⁷ *Alcmbic Club Reprints*, No. 14.

The investigation in question concerns the nature of the two isomeric compounds, tartaric and racemic (paratartaric) acid, to which reference has already been made.

To understand the steps which led to the remarkable results achieved by Pasteur it is necessary to revert to the year 1808 when Malus discovered the phenomenon of the polarization of light. At his death, which took place at the early age of thirty-seven, his pupils Arago and Biot continued his investigations on the subject. Biot (1815) observed the peculiar property which a section of quartz crystal exhibits, when cut parallel to the axis and viewed by polarized light, of producing rotatory polarization. He found, moreover, that there exist two kinds of crystals which rotate the beam of light in opposite directions. Some years earlier Hauy, the mineralogist, had noticed two kinds of quartz crystals possessing hemihedral facets on opposite sides of the crystal, constituting what are known as enantiomorphous forms. In 1820 Sir John Herschel suggested in a paper read before the Royal Society a possible link between the opposite kind of polarization and the reversed position of the facets.

The suggestion of Herschel recurred to Pasteur when in 1848 he discovered hemihedral facets on tartaric acid, which was known to be dextro-rotatory. He recalled at the same time a statement which Mitscherlich had communicated to the Academy of Sciences, and which had greatly puzzled him at the time of its publication, to the following effect: 'The sodium ammonium double salt of racemic and tartaric acids have the same chemical composition, the same crystal form, and the same angles, the same specific gravity, double refraction, and consequently the same angles between the optic axes. The aqueous solutions have the same refraction, but the dissolved tartrate turns the plane of polarization and the racemate is indifferent, as Biot has found for the whole series of salts, yet here the nature and number of the atoms, their arrangement and distances are the same in the two substances.'

If, thought Pasteur, the racemate should possess no hemihedral facets and Herschel's supposition is correct, it will account for its optical indifference.

He forthwith crystallized sodium ammonium racemate, but found that the crystals exhibited the hemihedral facets of the tartrate. On further examination it was observed that the facets were differently situated on the different crystals, some being disposed on the inverse side to others. The forms were enantiomorphous. They were separated, and the one proved to be the salt of ordinary or right-

handed tartaric acid, whereas the other was that of a new left-handed acid, and the presence of the two kinds in equal quantities produced inactivity in the solution.

In reviewing his results, Pasteur pointed out that the hemihedral facets in the crystal mark the property of rotatory polarization, but, whereas the property is present in crystalline quartz and absent in the amorphous variety, it is absent in solid tartaric acid, but present in the fused or dissolved state.

The asymmetry must therefore be a function of the structural arrangement of the *molecules* in quartz, and of the *atoms* in the molecules of substances which rotate the plane of polarization in the gaseous and liquid state or in solution. In the latter the molecules are asymmetric. Now where asymmetry exists in an object, such as a hand or foot, the only other object which is symmetrical with it is its reflected image, i. e. the corresponding hand or foot which cannot, however, exactly overlap. The object and image are said to be non-superposable. How is this asymmetry of the molecule, which may exist as object and image, produced? 'Are the atoms of right-handed tartaric acid,' asks Pasteur, 'arranged along the spiral of a right-handed screw, or are they situated at the corners of an irregular tetrahedron, or have they some other asymmetric grouping? We cannot answer these questions. But of this there is no doubt, the atoms possess an asymmetric arrangement having a non-superposable image. Equally certain is it that the atoms of the left-handed acid possess just the inverse asymmetric arrangement. Lastly, we know that racemic acid results from the juxtaposition of these two inversely asymmetric atomic groupings.'¹

Thus, the paths pursued by the French and German chemists, though they lay so far apart in point of time and differed so widely in their character, converged ultimately towards the same end, the conception of atomic space arrangement.

Whilst the closing words of Wislicenus' memoir were taking root in the mind of the brilliant young Dutch chemist, van 't Hoff, Pasteur's views were being moulded into definite shape by his countryman Le Bel. Almost simultaneously van 't Hoff and Le Bel published their theories of space- or stereo-chemistry. Van 't Hoff's paper appeared in September, 1874,² whilst Le Bel's memoir was published in November of the same year.³

¹ *Alcemic Club Reprints*, No. 14; *Ostwald's Klassiker*, No. 28.

² 'Voorstel tot Uitbreiding der Structuurformules in de Ruimte,' Brochure, 1874.

³ *Bull. Soc. Chim.*, 1874, 22, 337.

STEREOCHEMISTRY OF CARBON

Optical Activity and Asymmetry. The theory of van't Hoff and Le Bel connects optical activity with molecular structure. Substances which are optically active in the fused state or in solution contain within the molecule at least one multivalent atom united to different elements or groups forming an *unsymmetrical space arrangement*. As four is the minimum number of material points demanded by any space arrangement in three dimensions, the multivalent atom which unites the elements or groups must be at least tervalent. In the majority of carbon compounds the multivalent atom is carbon; but optically active compounds are known in which the central element of the system is nitrogen, sulphur selenium, or tin (pp. 168-171).

Optical Isomerism. Object and Mirror Image. As Pasteur pointed out, every asymmetrical object, like a hand or foot, has its fellow, but they do not precisely overlap; they are non-superposable. A left hand will not fit a right-hand glove. In the same way a substance containing a carbon atom, round which four different groups are distributed in three-dimensional space, is capable of existing in two forms which correspond to a left and right hand, or to an object and its reflected image.

The chief point of difference between two substances, having a space arrangement or *configuration* of their atoms corresponding to object and image, lies in their action on polarized light, the one turning it to the right (right-handed or dextro-rotatory), and the other, precisely the same amount, to the left (left-handed or laevo-rotatory) when in the dissolved or liquid state. In all other physical properties—density, molecular volume, boiling-point, melting-point, solubility, conductivity, refraction, &c.—and in their chemical behaviour the two substances are identical. There are numerous observations which support this conclusion. The two complementary active forms are variously termed *active components*, *antipodes*, or *enantiomorphs*. The term enantiomorph, though applied originally to crystal forms (p. 62), appears on the whole the most suitable and convenient. It conveys the idea of object and image, and it can moreover be used both in the singular and in the adjectival form of *enantiomorphous*. The dextro- or laevo-rotation of a substance is indicated by the letters *d* or *l* or by the plus or minus sign. So far the theories of van't Hoff and Le Bel substantially agree, but in points of detail they present certain differences.

Van't Hoff's Theory. Van't Hoff regards the carbon atom as possessing four valencies or bonds directed towards the summits of a tetrahedron, of which it occupies the centre. If the groups represented by a , b , c , d attached to these four bonds (Fig. 1) are different, such a grouping is present in substances, which, like active amyl alcohol or paralactic acid, exhibit optical activity.

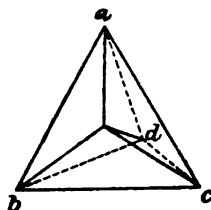
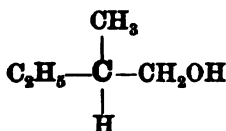
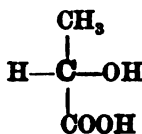


FIG. 1.

In amyl alcohol the central carbon atom is linked to the groups H , CH_3 , CH_2OH , and C_2H_5 ; in paralactic acid to H , OH , CH_3 , and $COOH$:



Amyl alcohol.



Paralactic acid.

Represented by space formulae (Figs. 2 and 3) the grouping is unsym-

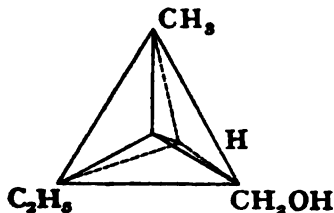


FIG. 2.

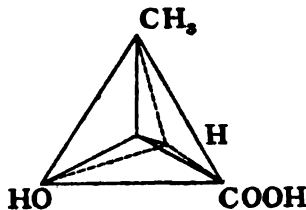
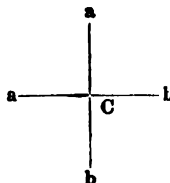
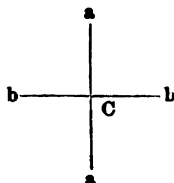


FIG. 3.

metrical, or asymmetrical in the sense that it forms a figure which cannot be divided in any direction into exactly similar halves.¹

¹ Van't Hoff points out the necessity of some such space arrangement if we desire to explain the absence of isomerism in cases where carbon is attached to two pair of similar groups Ca_2b_2 ; for if the arrangement is represented in one plane the two following forms should exist, and no such case of isomerism is known.



The same is true of the compound Ca_2bc which should form two structural isomers, but is represented by only one individual.

The central carbon atom of the group is termed the *asymmetric carbon atom*.

Such an asymmetrical group has a complementary form or mirror-image possessing the reverse rotation. The two forms of lactic acid will appear as in Fig. 4. The one is the mirror-image of the other and they cannot be turned so as to coincide. This can only be effected by interchanging two of the groups in one of the figures.

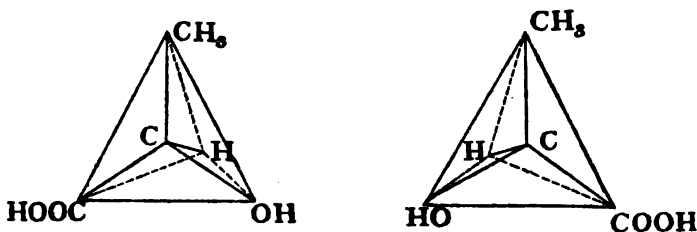


FIG. 4.

Van't Hoff used a tetrahedron to denote the distribution of the four groups, but did not postulate any special shape of tetrahedron, which may be regular or not, and will probably depend on the relation of the groups. The molecular dimensions in no way affect the main conclusions, and may for the present be disregarded. It is not, however, essential to make the asymmetric carbon the centre of a tetrahedral figure as van't Hoff proposed. The principle is in no way affected if the tetrahedron is replaced by a sphere on which the four groups are distributed in three-dimensional space, or if the groups are attached to four carbon linkages not lying in one plane, thus :

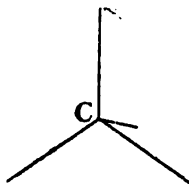


FIG. 5.

Le Bel's Theory. As already stated, in its fundamental idea Le Bel's theory agrees with that of van't Hoff. Both recognize the existence of asymmetry produced by a space arrangement of four different groups or radicals surrounding the central carbon atom, its effect in producing rotatory polarization, and the necessary consequence of a complementary form or mirror-image having the

reverse rotation. They differ in regard to the nature of valency. Le Bel does not recognize the structural conditions laid down by Kekulé's theory of the quadrivalency of carbon or van't Hoff's added hypothesis that the bonds are directed towards the summits of a tetrahedron. 'The asymmetry of the molecule,' says Le Bel,¹ 'can only be manifested by the asymmetric distribution of four atoms or radicals united to a single carbon atom, and this asymmetry will necessarily exist if these four radicals are different, whatever be the geometrical form of the molecule.' As van't Hoff's theory is in stricter conformity with modern conceptions of structural chemistry, we shall proceed to develop his view of stereoisomerism.

Nature of the Space Arrangement. The theory, as we see, involves the conception of fixed material points. Such a conception, according to van't Hoff, is not inconsistent with that of atomic motion, for, as the possibility of dissociation diminishes with decreasing temperature, the state of things at absolute zero is only to be explained by atomic mechanics; for intramolecular motion then ceases and the atoms must retain their positions by some force of repulsion which, he says, may possibly be electricity.²

The internal motion of the atoms may therefore be disregarded, and the centres about which they oscillate considered as a statical system of material points. How far the modern views of valency fit in with the idea of material points, whether the valency of carbon takes the form of a force acting in four directions or of one evenly distributed over the atom, whether it is determined by a tetrahedral figure of the carbon atom or depends upon the subdivision of the atom into smaller parts, it is not our intention to discuss. We are at present concerned with the experimental evidence upon which the theory rests.

Optically Active Compounds contain Asymmetric Carbon. According to the theory all optically active compounds contain an asymmetric carbon atom.³

The following are well-known examples of optically active substances containing one or more asymmetric carbon atoms, denoted in the formulæ by heavy type:—

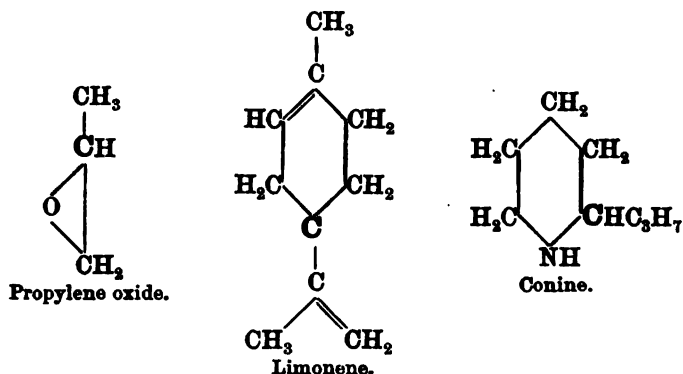
¹ *Bull. Soc. Chim.*, 1875 (2), 23, 888; 1882 (2), 37, 300; 1892 (3), 7, 164; see Freundler's *Stereochimie*, p. 10.

² *Arrangement of Atoms in Space*, by J. H. van't Hoff, trans. by A. Eilhart (Longmans), p. 6.

³ Excluding for the present derivatives of other elements than carbon.

Amyl alcohol	$\text{CH}_3(\text{C}_2\text{H}_5)_2 \cdot \text{CH} \cdot \text{CH}_2\text{OH}$
Lactic acid	$\text{CH}_3 \cdot \text{CH}(\text{OH}) \cdot \text{COOH}$
Malic acid	$\text{COOH} \cdot \text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{COOH}$
Chlorosuccinic acid	$\text{COOH} \cdot \text{CHCl} \cdot \text{CH}_2 \cdot \text{COOH}$
Asparagine	$\text{COOH} \cdot \text{CH}(\text{NH}_2) \cdot \text{CH}_2 \cdot \text{CONH}_2$
Aspartic acid	$\text{COOH} \cdot \text{CH}(\text{NH}_2) \cdot \text{CH}_2 \cdot \text{COOH}$
Leucine	$\text{C}_4\text{H}_9 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$
Mandelic acid	$\text{C}_6\text{H}_5 \cdot \text{CH}(\text{OH}) \cdot \text{COOH}$
Tyrosine	$\text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2 \cdot \text{CH}(\text{NH}_2) \cdot \text{COOH}$
Tartaric acid	$\text{COOH} \cdot \text{CH}(\text{OH}) \cdot \text{CH}(\text{OH}) \cdot \text{COOH}$
Mannitol	$\text{CH}_2\text{OH} \cdot (\text{CH} \cdot \text{OH})_4 \cdot \text{CH}_2\text{OH}$
Saccharic acid	$\text{COOH} \cdot (\text{CH} \cdot \text{OH})_4 \cdot \text{COOH}$
Glucose	$\text{CH}_2\text{OH}(\text{CH} \cdot \text{OH})_4 \cdot \text{CHO}$

The asymmetric carbon atom may also form part of a ring as in propylene oxide, limonene, and conine.



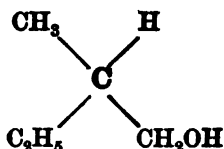
The supposed activity of a few compounds like propyl alcohol, $\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2\text{OH}$, and styrene, $\text{C}_6\text{H}_5\text{CH} : \text{CH}_2$, which contain no asymmetric carbon, has been traced to inaccurate observations.

Whether every solid compound, which is active in solution, crystallizes in a hemihedral form, as Pasteur supposed, is a question about which opinions at present differ, and until fresh evidence is forthcoming judgment must be suspended. Another question, however, suggests itself. Does activity of a substance in a liquid state or in solution necessarily involve activity of the solid? It appears to be rather the exception than the rule to find a substance active in both states. It has been observed in the case of certain tartrates, strychnine sulphate, zinc bimalate, and camphor. There is, however, no necessary connection between the activity of the two states,

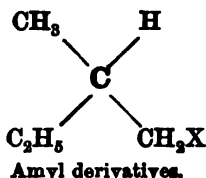
and it must be carefully borne in mind that stereoisomerism is concerned with the activity of the liquid or dissolved substance, and not with that of the solid.

Optical Activity and Asymmetry disappear together. According to the theory, activity should disappear with the removal of asymmetry, that is to say, when all the four groups are no longer dissimilar; when, for example, the compound Cabed becomes Ca_2bc .

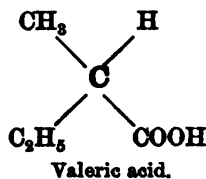
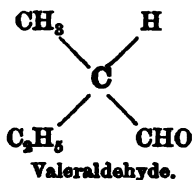
Amyl alcohol,



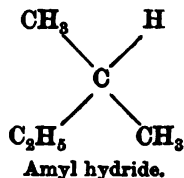
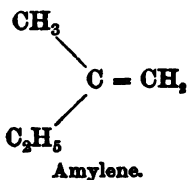
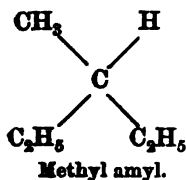
which is active in its esters, in the chloride, bromide, iodide, in amylamine and its salts, having the general formula :



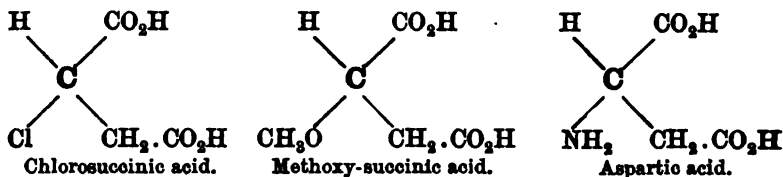
also in the aldehyde, valeric acid, and numerous other derivatives,



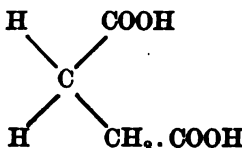
becomes inactive, as Le Bel and Just have shown, in methyl amyl, amylene, and amyl hydride, wherein the asymmetric carbon is lacking.



Active malic acid, which can be converted into active chlorosuccinic, methoxy-succinic, and aspartic acid,



yields inactive succinic acid on reduction,



Even living organisms which exhibit a tendency to form active substances never do so in the absence of an asymmetric carbon. Succinic acid, which often accompanies fermentative processes, is never active. It should be pointed out that where one group replaces another so that asymmetry is preserved, the product is not always active. The fact is accounted for by the compound undergoing during the process what is known as *racemisation*, which will be explained later (p. 80). Thus, an active chloro-succinic acid was obtained by Walden¹ from malic acid and phosphorus pentachloride, but the bromo compound prepared in a similar way was inactive. The same thing occurred with *l*-mandelic acid, which gave inactive phenylbromacetic acid. Observations of a similar character have frequently been made.

Optical Inactivity may exist with Asymmetry. We have now to discuss the converse of our first proposition. Is the presence of an asymmetric carbon atom always associated with optical activity? This is not necessarily the case. In the first place, the compound may consist of equal quantities of the two optically active varieties, in which case the activities will be neutralized, and hence the substance will appear inactive.

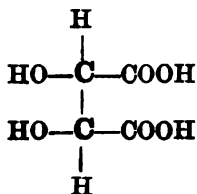
The Inactive Divisible Type. Thus, lactic acid from sour milk is inactive owing to the presence of equal quantities of the dextro- and laevo-compounds. Proof of this has been given by resolving the inactive acid into its two active components by methods to be presently described, and recombining the latter so as to repro-

¹ *Ber.*, 1893, 26, 214; 1895, 28, 1287.

duce the inactive substance. Inactive racemic acid is produced in the same way by dissolving equal quantities of the dextro and laevo tartaric acids. There exist a host of similar examples, which it is unnecessary to reproduce. In certain cases the two active varieties or enantiomorphs crystallize together, forming a product which has physical properties distinct from those of either constituent. Such a compound is called *racemic*. The term is derived from racemic acid, which in itself and its salts differs in crystalline form, water of crystallization, solubility, density, refraction, melting-point, &c., from either of the single active acids or their salts. Such differences disappear in solution, and the substance then behaves like a mixture. The distinction between racemic compounds and inactive mixtures is discussed more fully on p. 85. The two kinds of inactive substances are distinguished by the letters *r* and *dl*.

The Inactive Indivisible Type. There is another kind of inactivity which has quite a different origin. It depends upon the presence in the molecule of an even number of similar asymmetric carbon atoms, that is to say, carbon atoms to each pair of which a similar set of groups is attached. This inactive type was first observed by Pasteur in the case of tartaric acid which, in addition to inactive racemic acid, exists in the isomeric form of mesotartaric acid, and is obtained by heating ordinary tartaric acid with water or alkalis. The two are distinguished by different physical properties, but more especially by the fact that mesotartaric acid cannot be resolved into active components.

If we examine the structural formula of tartaric acid it will be seen that it possesses two asymmetric carbon atoms, denoted in the figure by thick type.



Each asymmetric carbon atom is attached to similar groups. Let us suppose that each asymmetric carbon with its associated groups produces a certain rotation in a given direction. We may imagine the following combinations of two similar asymmetric groups. Both produce dextro-rotation, or both produce laevo-rotation. They will represent the dextro- and laevo-enantiomorphs, and the mixture of the two will produce inactive racemic acid. Racemic acid is said to

be inactive by *external compensation*. Suppose, finally, that the two asymmetric groups produce rotation in opposite directions.

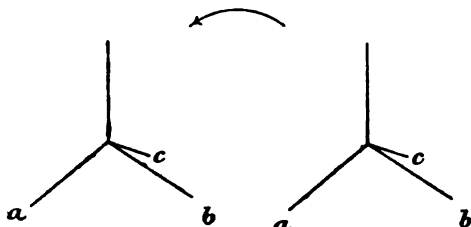


FIG. 6.

They will neutralize one another. The result will be a compound which is inactive by *internal compensation*. Such a compound cannot be resolved by any process into its active components. The last arrangement represents mesotartaric acid, which is permanently inactive or indivisible. The explanation is more easily followed by means of models. Suppose that Fig. 6 represents the two asymmetric carbon atoms and that the bonds lettered *a*, *b*, *c*, stand for the three groups H, OH, and COOH, for which coloured sticks may be employed. Join together two identical models by bringing the one on the top of the other (Fig. 7).

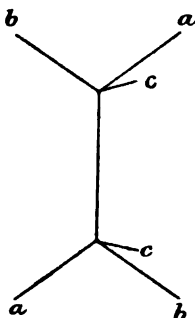


FIG. 7.

If we suppose each model to be dextro-rotatory, the combination will also be dextro-rotatory, and will stand for the dextro-acid, Fig. 8 (I).¹ The mirror-image of this is shown in Fig. 8 (II), and will represent

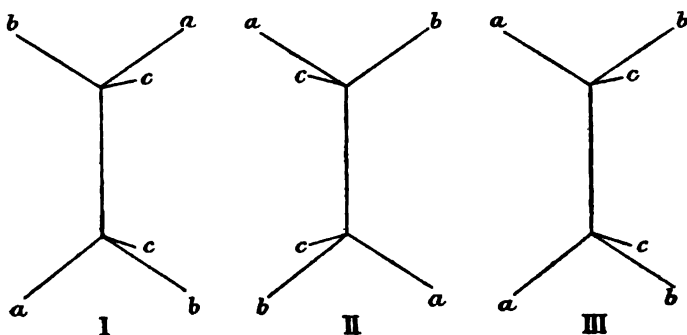


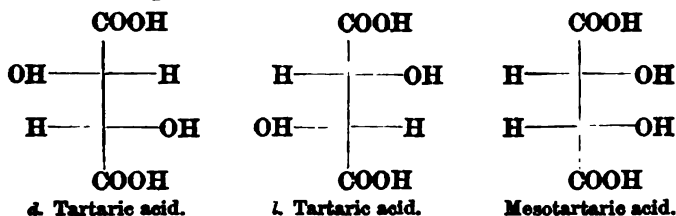
FIG. 8.

the laevo-acid. The mixture of the two will give inactive racemic

¹ It may be stated at once that there is no means of ascertaining the absolute relation of configuration to rotation.

acid. Finally, if the top and bottom asymmetric groups standing in the relation of object and image are combined, the rotations are opposed and neutralized and mesotartaric acid, Fig. 8 (III), is produced. It is identical with its mirror-image, for by revolving either of them in the plane of the paper through 180° they will coincide.

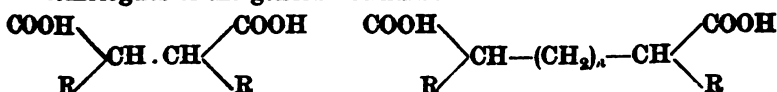
Instead of models, projection formulae can be used, and if the asymmetric carbon atom, instead of being represented by C, is merely denoted by a cross line, the above configurations will assume the following simple form :



The formulae unavoidably depict a fixed relative position of the two sets of groups surrounding the asymmetric carbon atoms ; but it must be remembered that the above theoretical results would follow, if either or both carbon atoms revolved on a vertical axis into any other position, or continued permanently in a state of oscillation or rotation, provided the relative positions of the members of each asymmetric group were retained. The fixity, or otherwise, of the groups is a question which will be discussed later (p. 188).

The correctness of the explanation, which accounts for the inactive indivisible type, follows from the researches of E. Fischer,¹ who has shown that inactive and indivisible mucic acid, $\text{CO}_2\text{H} \cdot (\text{CHOH})_4 \cdot \text{CO}_2\text{H}$, gives, on reduction, galactonic acid, $\text{CH}_2\text{OH} \cdot (\text{CHOH})_4 \cdot \text{CO}_2\text{H}$. The symmetry of the molecule is thus disturbed, and the new substance, which now belongs to the divisible inactive type, can be resolved into its active enantiomorphs (p. 74).

The number of examples of the inactive and indivisible or meso type is not very large. In addition to mesotartaric acid and mucic acid already mentioned, erythritol $\text{CH}_2\text{OH} (\text{CHOH})_2 \text{CH}_2\text{OH}$ and dulcitol $\text{CH}_2\text{OH} (\text{CHOH})_4 \text{CH}_2\text{OH}$ belong to the same class of inactive compounds, as well as the dialkyl derivatives of succinic acid and its homologues of the general formula :



¹ Ber., 1892, 25, 1247, 1260.

The following few examples afford a comparison of racemic (*r*) and meso (*i*) forms, from which it will be seen that the differences in physical properties are in the majority of cases well marked:¹

Substance.	M. P.		Density.		Affinity constant.	
	<i>r.</i>	<i>i.</i>	<i>r.</i>	<i>i.</i>	<i>r.</i>	<i>i.</i>
Tartaric acid	204°	140°	1.697	1.666	0.097	0.06
Dimethyl succinic acid	209	129	1.314	1.329	0.0191	0.0123
Diethyl succinic acid	192	129	—	—	0.0843	0.0245
Diisopropyl succinic acid	226	171	—	—	0.2255	0.0108
Diphenyl succinic acid	229	183	—	—	0.026	0.020
Dimethyl glutaric acid	140	128	—	—	0.0055	0.0055
Dimethyl adipic acid	140	75	—	—	0.0042	0.0042

Where the identity of the racemic compound has not been directly ascertained by resolving it into its enantiomorphs, the division into racemic and meso is determined by analogy with the tartaric acids, the higher melting-point being arbitrarily assigned to the racemic form. It is not by any means certain that this relation always holds, and it may happen that a reversal of melting-points may frequently occur. In the above table the racemic form has been ascertained by direct observation only in the case of tartaric acid.

Chemical as well as physical differences in racemic and meso compounds have also been observed, depending on solubility and water of crystallization. Whereas the calcium salt of mesotartaric acid crystallizes with three molecules of water $\text{CaC}_4\text{H}_4\text{O}_6 + 3\text{H}_2\text{O}$, that of racemic and the *d*- and *l*-acids crystallize with four.

Again, mesotartaric and racemic acid crystallize with one molecule of water, whereas the active tartaric acids are anhydrous. Hydrobenzoin $\text{C}_6\text{H}_5 \cdot \text{C}(\text{OH}) \cdot \text{C}(\text{OH}) \cdot \text{C}_6\text{H}_5$ is anhydrous, whilst isohydrobenzoin, the racemic form, may contain water of crystallization.

Resolution of Externally Compensated Compounds. The best proof of the existence of a substance (racemic compound or mixture) which is inactive by external compensation is its separation or resolution into active enantiomorphs. This is obviously a matter of some difficulty owing to the fact that stereoisomerism is only manifested by optical and occasionally crystallographic properties, and by the relation of the two enantiomorphs to other asymmetric substances. In all other respects the stereoisomers are identical. The three principal methods at present in use for resolving externally compensated compounds were suggested and developed by Pasteur.

¹ A more complete list will be found in Werner's *Lehrbuch der Stereochemie*.

Resolution by Crystallization in Enantiomorphous Forms.

The method has already been described in the case of sodium ammonium racemate (p. 62), and depends on the deposition of the two enantiomorphous crystalline forms of the *d*- and *l*-tartrates from solution,¹ which can be separated mechanically. The process has undergone an interesting development. Why, it may be asked, does not the salt of the original racemate crystallize? On evaporating solutions of sodium ammonium racemate Städel² did, in fact, obtain crystals of the original racemate, and not those of the *d*- and *l*-tartrates as Pasteur had done. How were the results to be reconciled? Scacchi³ solved the problem by showing that the formation of the one or other kind of salt is dependent on the temperature at which crystallization occurs. A high temperature favours the crystallization of the racemate, whilst at the ordinary temperature the two tartrates are chiefly formed. The temperature above or below which the transformation occurs was found by Wyruboff⁴ to be about 28°. Van't Hoff and van Deventer⁵ have since shown that the *transition temperature*, as it is now termed, lies between 26.7° and 27.7°, and is determined by the loss of water of crystallization from the tartrates and their conversion into the racemate according to the following equation :



Above the transition temperature the tartrates lose water of crystallization and the racemate is formed ; below this temperature water is absorbed and the tartrates are produced. The transition temperature has since been studied in the case of other substances,⁶ and great accuracy has been introduced into the observations by the refined methods of van 't Hoff, which are described in text-books of physical chemistry. The resolution of inactive substances by crystallization in this way has had only a limited application, owing to the difficulty of obtaining well-crystallized enantiomorphous specimens capable of mechanical separation. It has, however, been used by Purdie⁷ to resolve inactive lactic acid by means of the zinc-ammonium double salt, by Erlenmeyer jun.⁸ to separate racemic isohydrobenzoin, and by Körner and Menozzi⁹ to break up inactive asparagine. As all the substances named can be prepared artificially in their inactive

¹ Pasteur, *Ann. Chim. Phys.*, 1848 (3), 24, 442 ; 1850, 28, 56.

² *Ber.*, 1878, 11, 1752.

³ *Rend. Accad. Napoli* (1865), 250.

⁴ *Bull. Soc. Chim.*, 1884, 41, 210 ; 1886, 45, 52 ; *Compt. rend.*, 1886, 102, 627.

⁵ *Zeit. phys. Chem.*, 1887, 1, 165.

⁶ Kenrick, *Ber.*, 1897, 30, 1749.

⁷ *Trans. Chem. Soc.*, 1893, 68, 1143.

⁸ *Ber.*, 1897, 30, 1531.

⁹ *Gazz. chim.*, 1887, 226.

forms, their resolution into active constituents can be effected in this way spontaneously, and consequently without the direct intervention of vital, i. e. asymmetrical, influences, a view which is contrary to that upheld by Pasteur.

The other two methods of Pasteur are based on the different behaviour of the two enantiomorphs under what may be termed asymmetric conditions.

Resolution by the Biochemical Method. Pasteur (1860) observed that a solution of ammonium racemate containing a little potassium phosphate becomes laevo-rotatory after green mould (*penicillium glaucum*) has been grown in it. The rotation increased slowly until a maximum was obtained, when no more *d*-tartrate was left in solution. In other words, living organisms, which Pasteur regarded as asymmetric bodies, have the property of *selective assimilation*. The observation has been widely applied, and many of the lower vegetable organisms—bacteria, fungi, and yeasts—have been pressed into the service of the chemist. The process is usually conducted as follows:—A dilute and sterilized solution of the inactive substance in water is prepared, to which small quantities of nutrient materials, such as phosphates and ammonium salts, are added, and finally a pure culture of the organism. After keeping the solution at a suitable temperature for the growth of the organism, a portion is withdrawn from time to time and examined in the polarimeter until a maximum rotation is reached.

The curious observation has been made by P. Frankland and MacGregor,¹ that, although fresh cultures of *bacillus ethaceticus* act only upon the dextro-salts of glyceric acid, they can, by cultivation in a solution of calcium glycerate, be gradually induced to assimilate the laevo-enantiomorph as well, but this is an exception to the general rule. The different kinds of organisms which have been used for resolving inactive substances in the manner described above do not always assimilate the same enantiomorph; on the contrary, they show the greatest diversity in their tastes, one organism attacking the dextro- and another the laevo-enantiomorph in an apparently arbitrary manner. The loss of the one enantiomorph, as well as the usually small yield of active material, constitute the chief disadvantages of the process. On the other hand, the method can be applied to a great variety of compounds, such as acids, alcohols, and sugars, and is frequently used for finding if an inactive substance is capable of resolution. Examples of its application are very numerous,

¹ *Trans. Chem. Soc.*, 1893, 63, 1084.

lists of which will be found in papers by Winther,¹ McKenzie and Harden,² and in Werner's *Lehrbuch der Stereochemie*, p. 63.

Substance.	Organism.	Destroyed.
Racemic acid	penicillium	d.
	schizomycetes	l.
Lactic acid	penicillium	d.
	bacteria	l.
Mandelic acid	penicillium	d.
	aspergillus mucor	l.
	yeast	d.
	bacterium termo	l.
Glyceric acid	penicillium	l.
	bac. ethaceticus	l.
Ethoxy succinic acid	penicillium	d.
Methyl ethyl carbinol	penicillium	d.
Methyl propyl carbinol	penicillium	d.
	aspergillus niger	d.
Phenyl dibromopropionic acid	aspergillus fumigatus	l.
Amyl alcohol	fungus	l.
Propylene glycol	fungus	d.
	bacterium termo	d.
	bacterium from cheese	d.
Glucose, mannose, } galactose and fructose }	yeast	d.

The power of selective assimilation by living organisms finds a parallel in the different physiological action of enantiomorphs on the animal body and of the animal body on enantiomorphs. For instance, Piutti³ found that *d*-asparagine has a sweet taste, whereas that of the laevo-enantiomorph is insipid; *l*-nicotine, according to Pictet and Rotschy,⁴ is far more poisonous than the *d*-compound; whilst Chabrie⁵ showed that *l*-tartaric acid, when administered to guinea-pigs, was found to be twice as poisonous as the *d*-acid. The power of the human body to assimilate and excrete certain optically active substances belongs to the same order of phenomena.

Resolution by means of Active Substances. The third method of Pasteur is the one most commonly employed. Pasteur⁶ found that when racemic acid is combined with the active (laevo) base cinchonine and the solution left to crystallize, the cinchonine salt of *l*-tartaric acid is the first to separate. In order to explain the fact we must assume that if sufficient cinchonine is present two salts are formed, one of the alkaloid with the laevo-acid and the other with

¹ Ber., 1895, 23, 3022.

² Ber., 1896, 19, 1691.

³ Compt. rend., 1893, 116, 1410.

⁴ Ann. Chim. Phys., 1853 (3), 38, 437; Compt. rend., 1853, 37, 162.

⁵ Trans. Chem. Soc., 1903, 83, 424.

⁶ Ber., 1904, 37, 1233.

dextro-acid. If we denote the acid by *A* and the base by *B*, we obtain the following two combinations:—



The two compounds are not enantiomorphs, for the two acids of opposite rotation are united to the same active base. They consequently exhibit different properties, more especially different solubilities. It is thus possible to resolve, by fractional crystallization of their salts, inactive acids (e. g. racemic acid) when combined with the same active base (e. g. cinchonine), or inactive bases (e. g. conine) when united to the same active acid (e. g. tartaric acid). There are certain practical difficulties connected with the operation which are occasionally encountered, such as small differences in the solubility of the two salts or lack of crystallizing power.¹ The first may be overcome by substituting an active reagent of higher rotatory power, which usually enhances the differences in physical properties; the second by inoculating the solution with a crystal of a similarly active salt, so as to induce crystallization. The bases commonly used are the active alkaloids, quinine, quinidine, cinchonine, cinchonidine, strychnine, morphine, and brucine, and the active acids tartaric, camphorsulphonic, and bromocamphorsulphonic acid. There are some acids, like the amino acids, alanine, leucine, tyrosine, &c., which are too weak to form stable salts with the alkaloids, and cannot therefore be submitted to the process of fractional crystallization. E. Fischer² found a simple solution of the difficulty by introducing the strongly acid radicals benzoyl or formyl into the amino group, thereby converting a weak acid into a strong one. The benzoyl derivatives readily form crystallizable salts with the alkaloids, from which, after resolution into their enantiomorphs in the usual way, the acyl group is removed by hydrolysis.

Recent Methods of Resolution. The methods of Pasteur, which depend upon the differences exhibited by the components of an inactive substance under the influence of asymmetric (physical, chemical or biochemical) reagents, have undergone expansion in various directions. Among the physical methods is that of Kipping and Pope,³ who crystallized sodium ammonium racemate from solutions containing *d*-glucose, and obtained on the average an excess of the dextro-enantiomorph. Attempts to induce separation of the enantiomorphs by crystallization in a strong magnetic field, that

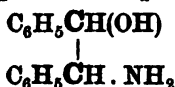
¹ Marckwald, *Ber.*, 1896, 29, 42.

² *Ber.*, 1899, 32, 2451, 3638; 1900, 33, 2370; *Ber.*, 1905, 38, 3997.

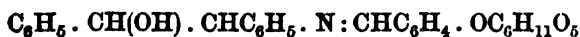
³ *Proc. Chem. Soc.*, 1898, 14, 113.

is, under conditions which ordinarily produce rotatory polarization in inactive materials, were made by Pasteur, and have since been repeated, but without success. Chemical methods have been employed by E. Fischer, Walden and Marckwald, and M^cKenzie. Fischer¹ examined the rate of hydrolysis of cane-sugar by *d*- and *l*-camphoric acid with negative results. A similar process has been studied with more success by Walden,² and Marckwald and M^cKenzie.³ The method is based on the different behaviour of the two enantiomorphs of an acid with the same active alcohol or of an alcohol with the same active acid, more especially in the effect on the rate of hydrolysis and esterification. The ester of the one combination is more easily formed or hydrolysed than the other, and therefore incomplete hydrolysis or esterification of the inactive material leads to a partial resolution of the enantiomorphs. If, for example, inactive mandelic acid is incompletely esterified with *l*-menthol, the dextro acid being more rapidly esterified, the unesterified portion is laevo-rotatory.

Erlenmeyer, jun.,⁴ has separated isodiphenyl hydroxyethylamine



by combining it with active helicin. The compounds of the formula



formed by the two enantiomorphs are not mirror-images, and can be separated by fractional crystallization, and Neuberg⁵ has succeeded in resolving racemic arabinose by crystallizing the hydrazone formed with *l*-menthylhydrazine. In this case nearly pure *d*-arabinose *l*-menthylhydrazone crystallizes from the alcoholic solution.

Among the methods which are related to Pasteur's biochemical method are the hydrolytic resolution of glucosides by enzymes (emulsin and maltase), which was investigated by E. Fischer,⁶ and is treated more fully on p. 846, and the hydrolysis of the esters of an inactive acid by the fat-splitting enzyme *lipase*, which was studied by Dakin⁷ (p. 858). Both observers found that the enzymes in question exhibit the power of selective hydrolysis. Thus Dakin showed that the partial hydrolysis of the inactive esters of mandelic acid results in the production of the dextro-rotatory free acid and a laevo-rotatory residue of unchanged ester.

¹ Ber., 1899, 32, 3617.

² Ber., 1899, 32, 2180; 1901, 34, 469.

³ Ber., 1908, 36, 1192.

⁴ Journ. of Phys., 1908, 30, 258; 1905, 32, 199.

⁵ Ber., 1899, 32, 2708.

⁶ Ber., 1908, 36, 976.

⁷ Zeit. physiol. Chem., 1898, 26, 61.

Substances which have not been resolved. Whilst a certain number of inactive externally-compensated compounds like asparagine, isohydrobenzoin, and certain lactones of saccharic acid show no tendency to form racemic compounds and separate spontaneously on crystallization into their enantiomorphs, and others again can be resolved more or less readily by the methods described, there still exists a large class of substances which up to the present have defied all attempts to divide them. No substance containing less than two carbon atoms united to an asymmetric carbon atom has been obtained in an active form.¹ Examples of such compounds are :

Chlorobromomethane sulphonic acid	$\text{CHClBrSO}_3\text{H}$
Bromoglycollic acid	CH(OH)BrCOOH
Aldehyde ammonia	$\text{CH(OH)NH}_2\text{CH}_3$
Bromonitroethane	$\text{CHBrNO}_2\text{CH}_3$, &c.

According to Victor Meyer the difficulty of resolving them is to be attributed to the great mobility of groups in these simpler molecular complexes and their consequent tendency towards intramolecular change. Another class of compounds which has not yet been resolved has already been mentioned, namely, the symmetrical dialkyl succinic acids and their homologues (p. 74). They contain two similar asymmetric carbon atoms, and, like racemic and meso-tartaric acid, exist in two inactive forms possessing different physical properties. One of the isomers should be separable into its enantiomorphs, but so far this has not been accomplished.

Racemisation. In the foregoing paragraphs the resolution of inactive substances has been described. The reverse process, whereby an active substance is rendered inactive, is frequently observed. It is termed *racemisation*, and is brought about by the conversion of one half of the active material into its enantiomorph. That the change is due to this cause, rather than to the formation of some structurally different and inactive compound, has been shown repeatedly by resolving the product of racemisation into its originally active constituents.

Racemisation is usually effected by rise of temperature. It was first observed by Pasteur² who obtained both racemic and mesotartaric acid by heating cinchonine *d*-tartrate to 170°. Jungfleisch³ modified and improved the method, heating tartaric acid with ten to fifteen per cent. of water in sealed tubes to 175° for several hours

¹ See van 't Hoff's *Arrangement of Atoms in Space*, trans. by Eiloart, p. 26.

² *Compt. rend.*, 1858, 37, 162.

³ *Bull. soc. chim.*, 1872, 18, 201.

and obtained considerable quantities of racemic and mesotartaric acid. The same process has been found to bring about the racemisation of aspartic, mandelic, isopropylphenylglycollic, and camphoric acid. Active pinene, limonene and phellandrene, active amyl alcohol, and many of its derivatives are rendered inactive by heating. Active lactic acid is converted at 150° into inactive lactide, and active quinic acid into inactive quinide. The presence of foreign substances frequently produces racemisation. *d*-Tartaric acid is easily converted into racemic and mesotartaric acid when boiled with a concentrated solution of caustic soda.¹ Caustic potash racemises active amyl alcohol, lactic acid, mandelic acid, and amygdalin. Active leucine, glutamic acid, and pyrrolidine carboxylic acid, when heated with baryta water, and *d*-valeric acid, limonene, and pulegone, heated in presence of strong sulphuric acid, lose their activity. The racemising action on tartaric acid of the oxides of iron and aluminium has been attributed to the catalytic action of these substances.² Racemisation seems to occur more readily when substances are in the act of formation than when already formed. That proteins when heated with baryta give inactive tyrosine, leucine, and glutamic acid, whereas hydrochloric acid produces active compounds, may be ascribed partly to the reagent and partly to the action on the nascent compound. In this connection the racemising of a substance during the replacement of one group by another, as Walden observed when malic acid is converted into bromosuccinic acid (p. 70), can be readily understood. The temperature of racemisation of some substances is quite low, and the change known as *autoracemisation* has even been found to take place spontaneously at the ordinary temperature. Walden³ observed a gradually decreasing rotation in the esters of *d*-bromosuccinic acid and *d*-phenyl bromacetic acid when kept for three or four years. During this period a few of the substances were completely racemised.

In other cases, such as the polyhydroxy-acids, where more than two asymmetric carbon atoms are present, racemisation on heating with water is never complete, but only a single asymmetric group is affected, and the process is known as *partial racemisation*.⁴ The subject, which is of special interest in relation to the formation of synthetic sugars, is more fully discussed on p. 802.

In this connection it is interesting to learn from the investigations of Winther⁵ that the racemisation of active tartaric acid by

¹ Meissner, *Ber.*, 1897, 30, 1574.

² Jungfleisch, *Compt. rend.*, 1877, 85, 805.

³ *Ber.*, 1898, 31, 1416.

⁴ For examples of racemisation see Chr. Winther, *Zeit. phys. Chem.*, 1906, 56, 466.

⁵ *Zeit. phys. Chem.*, 1906, 56, 466, 720.

the action of alkalis takes place in two stages; one asymmetric carbon is first affected and then the other, in other words, the change is from the active acid to the meso form and from the meso to the racemic compound, a condition of equilibrium being finally established between the two latter.

The mechanism of the process is capable of various interpretations. Van't Hoff¹ points out that in the conversion of one stereoisomer into the other, where the stability is slight, equilibrium will be attained when the inactive mixture is formed; for it follows from the complete mechanical symmetry of the two isomers that the tendency to conversion is equal in both, and consequently the one present in larger quantity will always be converted in larger quantity until equal quantities of each are present. Werner² has suggested an ingenious mechanical device for representing the phenomenon, which disposes of certain difficulties, such as a readjustment of the bonds, or the actual separation of the groups from the asymmetric

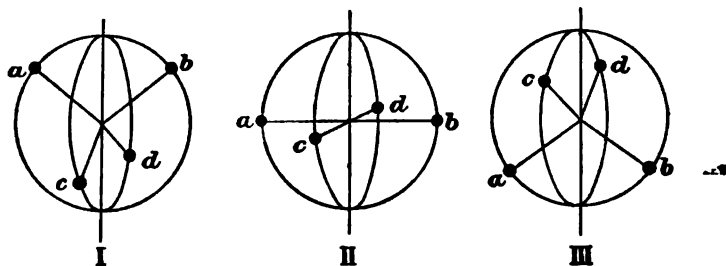


FIG. 9.

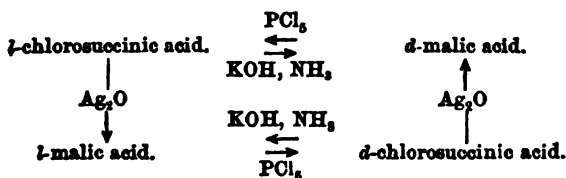
carbon during the rearrangement. He constructs a model consisting of two circular wires or discs soldered at right angles at the two ends of a common axis. Four differently coloured balls, pierced with holes, slip along each of the four wire semicircles into which the model is divided, and are retained in any position by elastic threads, which attach each ball to the centre of the common axis. The balls are arranged at the corners of an imaginary tetrahedron *a*, *b*, *c*, *d*, Fig. 9 (I). Racemisation is supposed to be effected by increasing the amplitude of the vibrations of each ball, that is, by moving it farther on each side of its original position along the wire semicircle. Each pair of balls may be supposed to eventually swing so far that at one moment they lie in the same horizontal plane, Fig. 9 (II). From this position, when the racemising agent is removed, the balls may return to their original, or pass over into opposite hemispheres, as shown in Fig. 9 (III). As there is an equal chance of both changes occurring, an

¹ *Ber.*, 1877, 10, 1620.

² Werner's *Stereochemie*, p. 48.

equal number of molecules of both kinds, that is, equal quantities of the two enantiomorphs, will be formed. That the second arrangement is the mirror-image of the first is easily demonstrated by turning the model Fig. 9 (III) upside down on its vertical axis.

Conversion of Active Compounds into Active Derivatives. The possibility of converting an active compound into an active derivative, provided molecular asymmetry is maintained, has already been advanced in support of the present theory (p. 70). The activity of the derivative is not, however, a necessary consequence of the change, seeing that racemisation may occur during the process, in which case an inactive derivative results. A curious phenomenon which has been observed in connection with the formation of active derivatives has at present received no satisfactory explanation. P. Walden¹ has shown that certain reagents produce derivatives which, although identical in structure, differ in their sign of rotation. It is known as *optical inversion*. Phosphorus pentachloride converts *l*-malic acid into *d*-chlorosuccinic acid, and *d*-malic acid into *l*-chlorosuccinic acid. Again, by replacing chlorine by hydroxyl in *l*-chlorosuccinic acid, using an alkali (potassium hydroxide or ammonia) as the reagent, *d*-malic acid is formed, but if silver oxide or water is employed the *l*-acid is obtained. Walden has studied the action of a variety of metallic oxides in the same way and has shown that they form a series, the end members of which produce diametrically opposite effects in the character and amount of rotation, whilst the intermediate members form products which in rotatory sign and value lie between the two extremes. The hydroxides of rubidium, potassium, ammonium, copper, cadmium, barium, lead, and sodium cause inversion in the sign, whereas those of silver, thallium, and mercury produce a malic acid having the same sign as the original chlorosuccinic acid. The following scheme taken from Walden's memoir shows the cycle of changes described above, from which it follows that the sign of rotation of the active chlorosuccinic and malic acids may be interchanged at will.

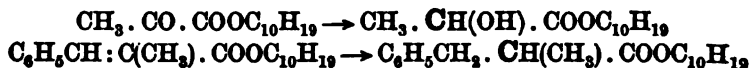


¹ Ber., 1895, 28, 2766; 1896, 29, 188; 1897, 30, 8151; 1899, 32, 1841. See also Tilden and Marshall, Trans. Chem. Soc., 1895, 67, 494; E. Fischer and Raske, Ber., 1907, 40, 1051.

Purdie and Williamson¹ have converted in the same way *l*-ethyl lactate by means of phosphorus chloride into *d*-chloropropionic ester. In this connection it may be pointed out that one enantiomorph may sometimes be converted directly into the other, for instance, *d*- into *l*-borneol by heating, and *l*- into *d*-menthol by the use of sulphuric acid.²

Asymmetric Synthesis. It was foreseen by the founders of the theory that asymmetric substances artificially produced from inactive materials would prove to be inactive. For it is clear from the identity in physical and chemical properties of the two enantiomorphs that there is no reason why a larger number of the one kind of molecules should be produced than of the other. This applies to the formation of an asymmetric carbon compound from a symmetric one, like bromopropionic acid from propionic acid, by substitution, or mandelic nitrile from benzaldehyde, by addition. It applies equally to the conversion of one asymmetric compound into another, such as inactive bromopropionic acid into lactic acid. Supposing, however, a new asymmetric carbon atom to be introduced into a compound which is already optically active, the question assumes another form. The new substance will be formed under asymmetric conditions, affording therefore the possibility of a product containing unequal quantities of the enantiomorphs relative to the new asymmetric carbon. E. Fischer was the first to show that this occurs in the formation of the synthetic sugars. For example, *d*-glucose forms two cyanhydrins in very unequal quantities, whilst *d*-mannose yields only one of the two possible derivatives.³

Attempts were made by Cohen and Whiteley⁴ to produce an active substance under asymmetric conditions by reducing the pyruvic and *α*-methyl cinnamic esters of *l*-menthol.



It was anticipated that on hydrolysis the product would be active, but only negative results were obtained. McKenzie⁵ was more successful and obtained from the menthyl ester of benzoyl formic acid by reduction, the ester of active mandelic acid, and from pyruvic ester, active lactic acid. He also succeeded in converting menthyl benzoyl formate by Grignard's method into the ester of phenyl methyl

¹ *Trans. Chem. Soc.*, 1896, 69, 829.

² Beckmann, *Annalen*, 1889, 250, 822.

³ Hartmann, *Annalen*, 1892, 272, 190.

⁴ *Trans. Chem. Soc.*, 1901, 79, 1305.

⁵ *Trans. Chem. Soc.*, 1904, 85, 1249.

glycollic acid, $C_6H_5 \cdot C(CH_3)(OH) \cdot COOH$, which gave an active acid on hydrolysis.

Racemic Compounds and Mixtures. It has already been stated (p. 70) that there are two classes of inactive substances which can be resolved into their enantiomorphs, and which, in the solid form at least, present considerable differences in their properties. They are known as racemic compounds (*r*) and mixtures (*dl*). They usually differ in crystal form, in the amount of water of crystallization, in density, solubility, and melting-point. The best-known example is racemic acid, and the active tartaric acids and their salts. Racemic acid and the racemates crystallize in holohedral forms, the tartrates form hemihedral crystals. Racemic acid contains one molecule of water of crystallization; the active tartaric acids are anhydrous. The solubility of racemic acid in water is greater than that of the tartaric acids.

As a rule the racemic compounds are less soluble, but it is not invariably so. *r*-Mandelic acid is more soluble than the active forms. The following are the melting-points and densities of some active and racemic types:

	Δ		m. p.	
	<i>dl</i>	<i>r</i>	<i>dl</i>	<i>r</i>
Malic acid	1.595	1.601	100°	180-181°
Tartaric acid	1.754	1.666	170	140
Chlorosuccinic acid	1.687	1.679	176	158-154
Mandelic acid	1.841	1.800	180	118-119
Camphoric acid	1.186	1.228	187	202-208

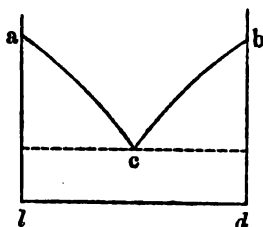
The evidence afforded by molecular weight determinations, both by the vapour-density and cryoscopic methods, as well as that derived from conductivity determinations, points to dissociation more or less complete of the racemic form into the inactive mixture on vaporisation or solution.

The criteria for distinguishing the two classes of compounds have been set forth in a very comprehensive manner by Bakhuis Roozeboom,¹ based on the phase rule. They are limited to the substances in the solid state, for there are no means at present available for distinguishing between inactive and racemic liquids. One method of Roozeboom consists in determining the melting-point of the substance under examination, and then adding a small quantity of one

¹ *Zeit. phys. Chem.*, 1899, 98, 494; see also *The Phase Rule*, p. 214, by A. Findlay, Longmans, 1904.

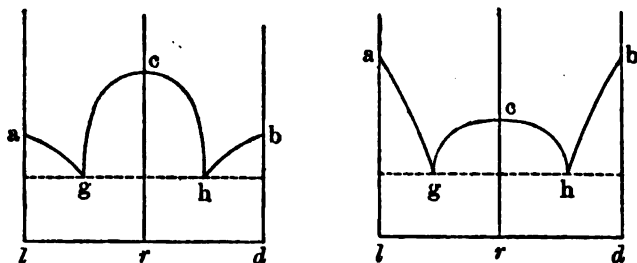
or other of the enantiomorphs. If a mixture is present, the melting-point will be raised ; if the substance is racemic it will be lowered. This result will be clear from the following considerations.

The melting-point curve of the mixture of two enantiomorphs will be represented by a descending and ascending curve; for as the two substances do not combine, although they possess the same melting-point, they may be regarded as distinct individuals, and consequently the addition of successive small quantities of the one enantiomorph will lower the melting-point of the other until an equal quantity of each is present. When the quantity of the second enantiomorph exceeds that of the first, the reverse change will occur and the melting-point will rise until the original melting-point is reached. If the quantities of laevo and dextro compounds be marked off on the horizontal *ld*, and the melting-points of the mixtures on the verticals *la* and *db*, the curve will follow the lines *ac*, *cb*, the minimum *c* representing equal quantities of the two enantiomorphs, that is, the inactive mixture.



It therefore follows that the addition of one or other enantiomorph to the inactive mixture will raise the melting-point.

In the case of a racemic compound, the addition of either enantiomorph will produce melting-point curves of the following character :



For there are three individuals concerned, the dextro and laevo enantiomorphs which possess the same, and the racemic compound which has usually a different (higher or lower) melting-point. The curve may, therefore, be divided into two parts, each of which may be

compared to the previous case of a simple mixture of two substances. If a represents the melting-point of the pure laevo compound, and c that of the racemic compound, and the percentages of the two be marked off on the horizontal ld , the curve will lie along ag , gc . The second half will be the counterpart of the first. By the addition of either enantiomorph to a racemic compound, the melting-point will consequently be lowered.

It is conceivable that the two enantiomorphs form neither a mixture nor a molecular complex, but are isomorphous and form mixed crystals. The effect on the melting-point produced by the addition of either enantiomorph will depend upon the composition of the mixed crystals which separate from the fused mass. If the crystals possess the same composition as the liquid mixture, the curve will be a horizontal line, and the addition of either enantiomorph will cause no change in the melting-point; otherwise it may produce a depression or rise, according to whether, on the addition of the active substance, the mixed crystals which separate from a mixture of the two enantiomorphs have a higher or lower melting-point than either constituent.

A second method proposed by Roozeboom for determining the character of the two classes of inactive substances is based on solubility. The saturated solution and the inactive material in contact with it are in equilibrium at constant temperature. If the inactive substance is a mixture, the addition of either enantiomorph will not affect the number of phases, and no change in solubility will occur. If the inactive material is a racemic compound, the addition of one of the enantiomorphs will introduce a new solid phase, and an alteration in the concentration of the solution will result. This method may be combined with the use of the polarimeter. In the first case there is no change in the solution and it will remain inactive, in the second case the solution will contain a certain amount of active substance which will be revealed by the polarimeter.¹

Partially Racemic Compounds. In addition to racemic compounds which are formed by the union of optical enantiomorphs, other active substances which are not structurally related may also crystallize together in the form of double salts. The phenomenon was first observed by Pasteur, who obtained crystals of the ammonium salt of *d*-tartaric acid in combination with an equimolecular proportion of the acid ammonium salt of *l*-malic acid. Another form of combination to which Ladenburg² has given the name of *Partially*

¹ See Findlay's *Phase Rule*, p. 278.

² *Ber.*, 1898, 31, 524, 937, 1969; 1899, 32, 50.

Racemic Compounds has been observed in the case of pyrotartrate of quinine, which forms three series of salts, from one of which the *d*-acid, from a second the *l*-acid, and from the third the inactive acid was separated. The quinine in the third case must therefore have combined with the unresolved racemic acid. Another partially racemic salt with an inactive base was prepared by Pope¹ from *r*-tetrahydropapaverine and *d*-tartaric acid.

The Number of Stereoisomers. The number of possible stereoisomers increases with that of the asymmetric carbon atoms. We have seen that if one asymmetric carbon atom is present, two stereoisomers exist; if there is a second asymmetric carbon atom which is structurally dissimilar from the first, four stereoisomers are possible. Denoting the asymmetric carbon atoms by A and B, and the rotation by + and -, the following four combinations may be formed:

1. + A	2. + A	3. - A	4. - A
+ B	- B	+ B	- B

of which 1, 4 and 2, 8 are enantiomorphous pairs. The trihydroxyaldehydes (erythroses) furnish an example, although only three out of the possible four are actually known,



With three asymmetric carbon atoms A, B, C, eight stereoisomers are possible, which may be derived from the above four by adding + C and - C alternately to each member.

1. + A	2. + A	3. + A	4. + A
+ B	+ B	- B	- B
+ C	- C	+ C	- C
5. - A	6. - A	7. - A	8. - A
+ B	+ B	- B	- B
+ C	- C	+ C	- C.

The enantiomorphous pairs in this case are evidently 1, 8; 2, 7; 3, 6; 4, 5.

With four asymmetric carbon atoms A, B, C, D the number of stereoisomers is increased to sixteen, for each of the foregoing yields two derivatives by adding + D and - D, as follows:

A	+	+	+	+	+	+	+
B	+	+	+	+	-	-	-
C	+	+	-	-	+	+	-
D	+	-	+	-	+	-	+
	1	2	8	4	5	6	7
							8

¹ *Trans. Chem. Soc.*, 1898, 73, 902.

A	-	-	-	-	-	-	-
B	+	+	+	+	-	-	-
C	+	+	-	-	+	+	-
D	+	-	+	-	+	-	+
	9	10	11	12	13	14	15

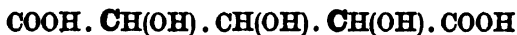
Thus the number of stereoisomers, in which n represents that of the asymmetric carbon atoms, is given by the expression 2^n . Examples of stereoisomers with three and four carbon atoms are given in the chapter on sugars (p. 816), where the method of determining their configuration is also discussed.

If the asymmetric carbon atoms are not structurally distinct, as in the case of tartaric acid (p. 71), the above expression must be modified, for the inactive indivisible type is introduced and the number of active forms is consequently fewer. Thus, if A and A represent two similar asymmetric carbon atoms, the following combinations may occur:

1. + A	2. + A	3. - A	4. - A
+ A	- A	+ A	- A

It is obvious from what has been previously explained that 2 and 3 are identical and correspond to the meso type (p. 71). Thus, instead of four, the number of stereoisomers is reduced to three, namely, two active and one inactive, by internal compensation.

Pseudo-asymmetry. If there are two similar asymmetric carbon atoms attached to a central carbon, which, in addition, binds two different groups as in trihydroxyglutaric acid,

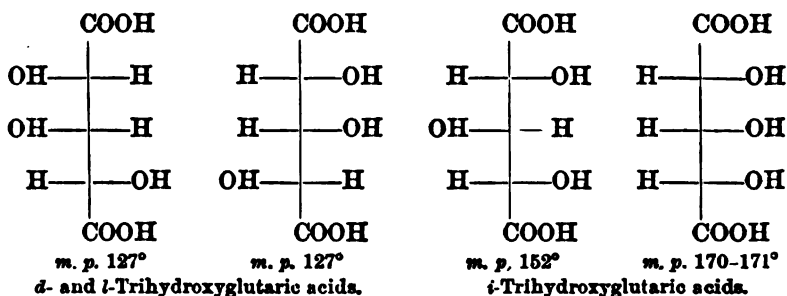


the problem becomes more involved. If A and B represent as before the asymmetric carbon atoms and C the central carbon atom, the following combinations are possible. Let us assume, in the first place, that the end groups A and A have the same configuration, that is, are both + or both -; they are identical, and the central carbon C possesses no asymmetry. Suppose, however, that the end groups have a different sign, two things happen; the activity of the end carbon groups is neutralized, but, at the same time, the central carbon atom becomes asymmetric and can exist in enantiomorphous forms. Four stereoisomers are thus possible, two active and two inactive, belonging to the meso type. They may be denoted by the following scheme,

in which O stands for absence of central asymmetry, and +C, -C for enantiomorphous configuration of the central carbon :

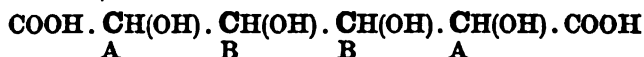
1. +A	2. -A	3. +A	4. +A
O	O	+C	-C
+A	-A	-A	-A

Experiment in the case of the trihydroxyglutaric acids supports this conclusion, for there are four stereoisomers, namely, two active and two inactive, which will probably have the following configurations :



The case is a curious one, for, although the central atom C in the two inactive forms has no effect on the sign of rotation, it produces, by virtue of the difference in configuration, a change in the properties. This form of asymmetry is known as *pseudo-asymmetry*.

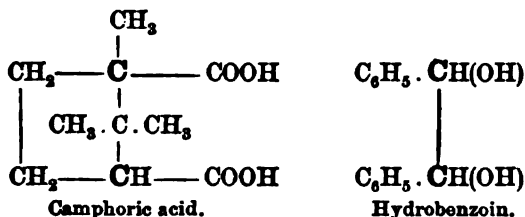
Stereoisomers with two pairs of Asymmetric Carbons. If the two end and two central carbon atoms of an open chain form two pairs of structurally similar asymmetric groups, A and B, as in the saccharic acids,



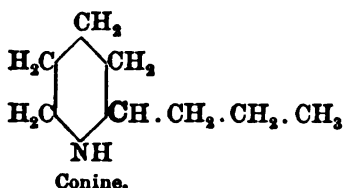
the number of isomers is no longer represented by the expression 2^n , which would give sixteen in the present case, but is reduced to ten. For when A, A and B, B have opposite signs inactive forms are produced of the meso type, which reduces the number by two, whilst each outer or inner pair may separately form a neutral group, which reduces it by four more. In the scheme on pp. 88, 89, configurations 4, 13 and 6, 11 become meso forms and represent two stereoisomers, whilst 2, 9; 8, 14; 5, 12; 8, 15 contain one neutral group and represent four instead of four pairs of stereoisomers.

Asymmetric Carbon in Cyclic Compounds. The optical activity of cyclic compounds has been traced to the same cause as that which

determines the rotation of open chain compounds, namely, the presence of an asymmetric carbon atom. The asymmetric carbon may form part of the ring, as in camphoric acid, or be present in the side-chain as in hydrobenzoin.



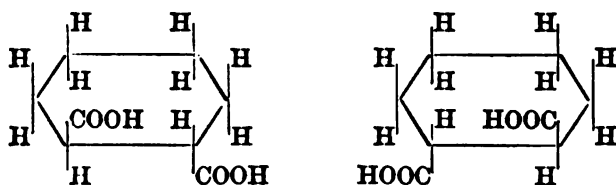
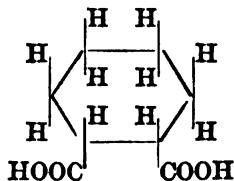
Stereoisomerism is manifested in the same manner as in open chain compounds, the only difference lying in the unusually larger rotation caused by the cyclic formation. If one asymmetric carbon atom is present as in conine, two optical enantiomorphs exist.



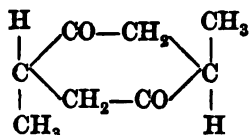
If two structurally different asymmetric carbon atoms are present, as in camphoric acids, two pairs of enantiomorphs (*dl*-camphoric and *dl*-isocamphoric acid (p. 516)) are produced. If the two asymmetric carbon atoms are structurally similar two active forms (*dl*-isohydrobenzoin) and one meso form (hydrobenzoin) can exist. The case is in fact precisely analogous to that of the tartaric acids. The symmetrical dialkyl succinic acids which exist in two inactive (racemic and meso) forms (p. 74) find a counterpart in the hexahydrophthalic acids (see p. 182). But, unlike the alkyl succinic acids, the racemic form of hexahydrophthalic acid¹ has been resolved into its enantiomorphs.

For simplicity the two enantiomorphs and the meso form of hexahydrophthalic acid are represented by hexagons, which must be viewed as if in perspective, that is, in a plane at right angles to that of the paper. The angles are occupied by the carbon atoms (omitted), to each of which two bonds are attached at right angles to the hexagonal surface.

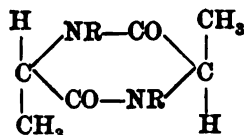
¹ Werner and Conrad, *Ber.*, 1899, 32, 3046.

*d*- and *l*-Hexahydrophthalic acids.*i* Hexahydrophthalic acid.

Pseudo-symmetry in Cyclic Compounds. A curious example of an inactive indivisible type is afforded by the diketohexamethylene derivatives and the diketopiperazines of the following formulae¹:

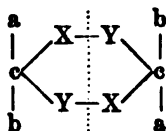


Dimethyl diketocyclohexane.



Dimethyl diketopiperazine.

They possess the general structure:



Now such a compound contains two structurally similar asymmetric carbon atoms, and, although strictly without any plane of symmetry, its reflected image is identical with it. Yet it does not accord with the meso type, since the two halves divided by the dotted line do not stand in the relation of object and image.

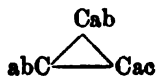
Attention was first drawn to the exceptional character of this configuration by Ladenburg,² who called the plane of symmetry *pseudo-symmetrical*, or, according to Groth, *compound symmetrical*. It divides the compound into halves, which become object and image when one half is revolved through 180°. Compounds which

¹ The ring and the attached groups are assumed to be in planes at right angles to one another, as previously explained.

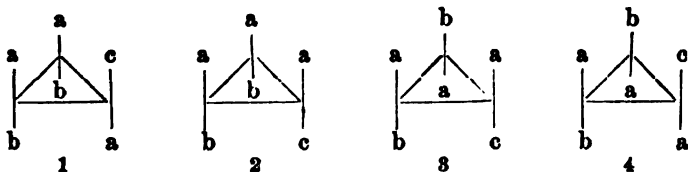
² *Ber.*, 1893, 23, 1996.

exhibit pseudo-symmetry in structure represent an inactive indivisible type.

Pseudo-asymmetry in Cyclic Compounds. Pseudo-asymmetry of the character of the trihydroxyglutaric acids (p. 89) is afforded by cyclopropane derivatives of the general formula:

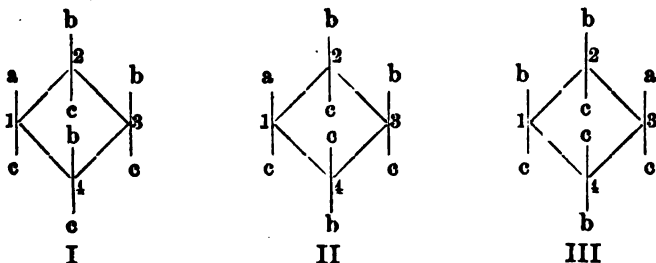


It may stand for the following configurations, in which the carbon atoms of the ring are represented as situated at the corners of a triangle lying at right angles to the plane of the paper:



Models illustrating these configurations may be easily constructed out of triangles of cardboard by thrusting pins through the corners. The head and point of the pin may stand for a, b, whilst c may be indicated by touching one point with coloured sealing-wax. Other cyclic configurations can be made in the same way from squares, pentagons, &c., of cardboard.

The first two of the above figures correspond to inactive meso compounds; the last two are optical enantiomorphs. The reasoning is the same as that which accounts for the existence of four trihydroxyglutaric acids. An example of this kind of isomerism is furnished by the three inactive 2, 5-dimethylcyclopentane 1-carboxylic acids of J. Wislicenus,¹ which probably represent one racemic and two meso forms. Another curious example of stereoisomerism referred to by Werner² is furnished by a cyclobutane ring of the following types:

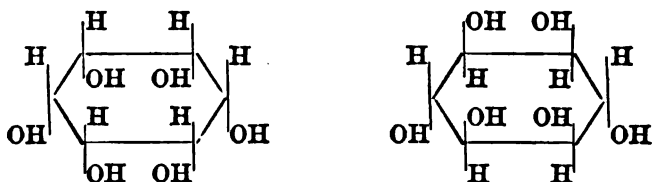


¹ Ber., 1901, 34, 2572.

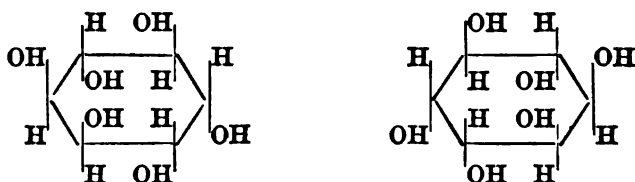
² Werner's *Lehrbuch der Stereochemie*.

The cyclic carbon atoms 2 and 4 are asymmetrical *per se*; 3 is symmetrical though structurally identical with 2 and 4. It follows from what has been stated above that 1 and 5 are pseudo-asymmetric, that is to say, it is a case of a double trihydroxyglutaric acid, and there may consequently exist four inactive meso compounds by interchanging separately a and c and b and c in I, and also two racemic compounds derived from II and III by interchanging one of the groups a, c or b, c.

Optical Activity with Pseudo-asymmetry. Finally, a form of pseudo-asymmetry causing optical activity has been pointed out by van't Hoff in the case of the inositols. Ordinary inositol from beans and flesh is a meso compound, and, therefore, has a symmetrical configuration of either of the following forms :



There are in addition *d*- and *l*-inositol ($\alpha_D = \pm 65^\circ$) obtained by Maquenne¹ from pinite (methyl *d*-inositol) and quebrachite (methyl *l*-inositol) to which van't Hoff attaches the following space formulae, corresponding to a non-superposable object and image :



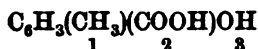
The relation of cyclic compounds to what is known as 'geometrical' or 'cis-trans' isomerism is discussed in a later chapter (p. 125).

Activity of Benzene Derivatives. The question as to whether the unreduced benzene molecule, without asymmetric carbon in the side-chain, could under any conditions be rendered asymmetric, and consequently optically active, has frequently been the subject of experimental investigation. Le Bel² attempted to resolve *o*-tolui-

¹ *Ann. Chim. Phys.*, 1891 (6), 22, 264; *Compt. rend.*, 1889, 109, 812.

² *Bull. Soc. Chem.*, 1882 (3), 38, 98.

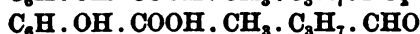
dine; Lewkowitsch¹ has done the same with *m*-homosalicylic acid,



and *o*-homo-*m*-hydroxybenzoic acid,



whilst V. Meyer and Lühn² have employed nitro- and aldehydo-thymotic acids for the purpose.



In no single case was the attempt successful. It may be further added that no simple benzene derivative showing optical activity has been found among the many products of this class elaborated by living matter.

Numerical Relation of Rotatory Power to Structure. In passing from the qualitative to the quantitative character of rotatory power it is necessary to consider first the conditions under which a comparison between the rotation of compounds may be instituted and the kind of errors which may arise. The usual method for determining rotation is to place the substance, if liquid, in the polarimeter tube at a given temperature or series of temperatures, and to read off the amount of deviation. From the data so obtained

the *specific rotation*³ is computed according to the formula $[\alpha]_D = \frac{\alpha}{d \times l}$.

In following this plan it should be remembered that some liquids, like alcohol, acetic acid, acetonitrile, acetone, &c., are bimolecular in the liquid state, and it is therefore necessary to determine the molecular complexity or degree of association of the substance beforehand. In comparing a series of related substances it may, however, be assumed that under similar conditions the molecular complexity is the same, and also that the larger molecular complexes are less disposed to associate than the simpler organic compounds. In examining a solid, which cannot conveniently be fused, a solvent is required, and the solvent may seriously affect the rotation.

¹ *Trans. Chem. Soc.*, 1888, 53, 781; *Ber.*, 1888, 16, 1576.

² *Ber.*, 1895, 28, 2795.

³ α is the observed rotation, l the length of the column of liquid in decimetres, and d the density, or, in other words, the specific rotation is the deviation produced by 1 gram of active substance in 1 cubic centimetre viewed through a column 1 decimetre in length illuminated with the sodium flame. The molecular rotation is determined from the specific rotation by multiplying by the molecular weight and dividing by 100 or $[\alpha]_D = \frac{[\alpha]_D M}{100}$.

We will consider first the simpler case, in which a solvent is unnecessary, and where the liquid or fused substance is directly examined.

Activity of Homologous Series. The effect of the active radical in a homologous series seems, as a rule, to be influenced by the first term or terms, and then to remain nearly constant in the succeeding members; in other words, the active group is chiefly affected by the group in its proximity. Tschugaeff¹ has made the following series of observations:

$$\text{Menthol } [\alpha]_D = -78.0^\circ$$

	$[\alpha]_D$		$[\alpha]_D$
Menthyl formate	-146.3°	Menthyl n-valerate	-157.3°
" acetate	-157.3	" n-caproate	-157.7
" propionate	-160.2	" n-heptate	-157.7
" n-butyrate	-156.9	" n-caprate	-155.8

A similar result was obtained by Rupe² with a series of unsaturated esters.

Menthyl ester.	$[\alpha]_D$	Menthyl ester.	$[\alpha]_D$
$\alpha \beta$ Pentenic acid	-177.1°	$\alpha \beta$ Hexenic acid	-173.4°
$\beta \gamma$ " "	-172.5	$\beta \gamma$ " "	-164.1
$\gamma \delta$ " "	-160.2	$\gamma \delta$ " "	-153.5
		$\delta \epsilon$ " "	-154.4

In both of the above tables it will be seen that the optical influence of an inactive constituent is stronger the nearer it approaches the asymmetric complex.³ Unsaturated compounds have usually a higher rotation than the corresponding saturated compounds.⁴

Activity of Cyclic Compounds. It is perhaps difficult to institute a satisfactory comparison between open and closed chain compounds, but on the whole it may be affirmed that the latter show an enhanced rotation. Anhydrides and lactones show a much higher rotation than the acids from which they are obtained. Lactide, $[\alpha]_D = -86^\circ$, is obtained from lactic acid, $[\alpha]_D = +8^\circ$. It is, therefore, scarcely surprising that the presence of a cyclic radical should produce a corresponding effect. Haller and Desfontaines⁵

¹ Ber., 1898, 31, 864.

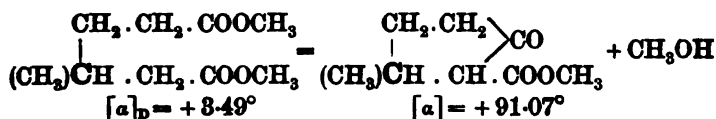
² Annalen, 1908, 327, 157.

³ Further examples are given in Landolt's *Optische Drehungsvermögen*, p. 259.

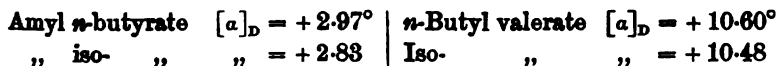
⁴ Walden, *Zeit. phys. Chem.*, 1896, 20, 580.

⁵ *Compt. rend.*, 1905, 140, 1205.

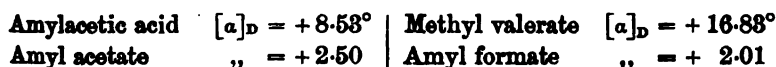
have converted a series of β -methyladipic esters into methylcyclopentanone carboxylic esters and found in each case a largely increased rotation:



Activity of Structural Isomers. No general rule determining the relation of activity to structural isomerism can be laid down, seeing that the sign and value of the rotation is influenced by the nature and, more especially, the position of the groups. This would follow from the facts contained in the paragraph on homologous series. The normal and iso-esters of active amyl alcohol, on the one hand, or active valeric acid, on the other, show very small differences:



But amylacetic acid differs considerably in rotation from amyl acetate, and methyl valerate from amyl formate:



Activity of Position Isomers. Conditions similar to those which determine the activity in a homologous series appear to obtain where the effect of the *o*-, *m*- and *p*-positions on the rotation of an active radical is considered, that is to say, the group nearest to the active radical usually produces the largest effect. The following are the molecular rotations of a series of menthyl esters of *o*-, *m*- and *p*-isomers. It will be seen that the increase or decrease in rotation is usually greatest with the ortho-compound.¹

Menthyl benzoate $[M]_D = -236.3^\circ$.

	Menthyl toluate.	Menthyl chlorobenzoate.	Menthyl bromobenzoate.	Menthyl nitrobenzoate.
ortho.	-231.2°	-195.0°	-205.3°	-281.2°
meta.	-240.8	-236.9	-233.7	-251.1
para.	-252.4	-237.3	-238.8	-234.8

¹ Tschugaeff, *Ber.*, 1898, 31, 1775; Cohen and Armes, *Trans. Chem. Soc.*, 1906, 87, 1192.

Activity of Stereoisomers. In spite of similarity of structure and molecular dimensions the effect on the rotation of the same optically active substance by the introduction of stereo- or geometrical-isomeric radicals¹ is very marked. Walden² has made a series of observations on the active amyl esters of fumaric and maleic acid and their derivatives, of racemic and mesotartaric acid and of *r*- and *i*-dimethylsuccinic acid.

	$[\alpha]_D$		$[\alpha]_D$
Fumaric ester	+5.98	Bromofumaric ester	+5.99
Maleic "	+4.62	Bromomaleic "	+4.58
Chlorofumaric ester	+5.78	Mesaconic "	+5.98
Chloromaleic "	+4.08	Citraconic "	+4.14
Racemic "	+8.87	Dimethyl succinic (r)	+8.66
Mesotartaric "	+4.77	(i)	+8.42

Activity of Solutions. The part which the solvent plays in modifying the activity of the dissolved substance is frequently so very marked that great caution must be exercised in drawing conclusions from the observed deviations.

Non-electrolytes. Some substances, like turpentine oil, nicotine, and ethyl tartrate, seem to be very little affected by the presence of a solvent. The specific rotation, calculated from observations of the pure liquid or of the solutions of different strengths in alcohol, acetic acid, and benzene, gives the same result. In other cases the influence of the solvent is very great. For example, ethyl *l*-mandelate in acetone, $[\alpha]_D = -90.6^\circ$, in chloroform -180° , although the molecular weight in both solvents is normal. The effect of the solvent on the magnitude of the rotation depends also on both temperature and concentration. Biot³ observed that an aqueous solution of tartaric acid shows an increase in specific rotation, with decreasing concentration, and he found later that camphor in alcohol or acetic acid exhibits the reverse phenomenon. Landolt⁴ says, 'this has since been substantiated for a very great number of substances. . . . So far we do not recognize any connection between the direction of this variation and the chemical nature of the active substance.' Since this paragraph was written the observations on the effect of both temperature and concentration on the rotation of active substances in different solvents have

¹ Geometrical isomerism is explained on p. 106, et seq.

² *Zeit. phys. Chem.*, 1896, 20, 877.

³ *Mém. de l'Acad.*, 15, 98; *Ann. Chim. Phys.*, 1844 (3), 10, 885.

⁴ *Optical Activity and Chemical Composition*, p. 20.

accumulated, and brought us a little nearer to a satisfactory generalization¹; at least, a general principle has been evolved which connects the solution volume and molecular aggregation of the active solute with its rotation, so far as it regards non-electrolytes.

Electrolytes. The observation of Oudemans and Landolt that the solutions of salts of active acids and bases attain a constant value with dilution, is a natural consequence of the theory of electrolytic dissociation to which Hadrich² first drew attention. Landolt³ found that equivalent quantities of different tartrates in dilute solution possess the same rotation independently of the metal present, whilst Oudemans⁴ obtained the same result with salts of the active alkaloids. From this generalization, which is known as the law of Landolt-Oudemans, it naturally follows that the rotation of an active salt, composed of both active acid and base, depends upon the combined activity of the two ions, a result which has been confirmed by Walden from the behaviour of the α -bromocamphor-sulphonates of morphine and cinchonine.

The change of sign in the rotation of malic and tartaric acids on dilution cannot be explained in this way, and it has been attributed to the presence of molecular aggregates in the concentrated solution of opposite rotation, just as crystal aggregates of a compound have been found which differ in sign from their solutions. Imperfect electrolytes, like the organic acids, exhibit in solution a series of changes which depend generally on the degree of dissociation. The extent of dissociation is increased by dilution and by rise of temperature, with a corresponding numerical change in rotation. The effect of different solvents may also be accounted for on the dissociation hypothesis.

Influence of Added Substances. The presence of inactive inorganic compounds sometimes influences the rotation of an inactive substance in a very sensible degree. It may be due to various causes, to an alteration in the degree of dissociation, to dynamic isomerism (see p. 172), to the formation of new compounds, or to some unexplained change in constitution. The activity of tartaric acid is increased three to four times by the addition of boric acid, and many of the polyhydric alcohols are affected in the same manner. The change

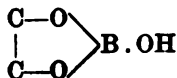
¹ Patterson, *Trans. Chem. Soc.*, 1900, 79, 167, 477; 1902, 81, 1097, 1184; 1904, 85, 765, 1148; 1905, 87, 88, 818, and Winther, *Zeit. phys. Chem.*, 1906, 55, 8; Walden, *Ber.*, 1906, 38, 845.

² *Zeit. phys. Chem.*, 1898, 12, 476.

³ *Ber.*, 1878, 6, 1077.

⁴ *Annalen*, 1879, 197, 48; 1881, 209, 88; *Rec. Trav. Chim. Pays Bas*, 1884, 1, 18; 1886, 4, 166. Tykociner, *Rec. Trav. Pays Bas*, 1, 144.

in this case is attributed to the formation of a ring structure which corresponds with its chemical and physical behaviour, and its enhanced rotation.¹ The ring formation will be of the following type, in which the hydrogen atoms of two hydroxyls are replaced by attachments to the boron atom :



The increased activity which tartaric acid and the tartrates undergo on conversion into tartar emetic, and the alkali boryl and arsenyl tartrates, is accounted for in the same way. The addition of molybdates, tungstates, and uranyl salts² greatly increases the rotation of malic and tartaric acid, and is probably due to the formation of complex acids depending apparently on the presence of a CH(OH) group, for no increase occurs in the chloro- and bromo-succinic acids where the group is absent.

Mutarotation. It has long been known that freshly prepared solutions of certain sugars change in rotation on standing. The specific rotation of glucose sinks to one-half before becoming constant. The phenomenon was therefore termed *birotation*. But when the rotation of other sugars was found to diminish to a less extent than one-half, whilst that of maltose was observed to increase on standing, the name was changed from *birotation* to *multirotation*. As the latter term implies some simple ratio between the original and final values the word *mutarotation* recently adopted by Lowry, which postulates neither increase nor decrease in any special ratio, but merely indicates a change in either sense, is to be preferred. The following table shows the initial and final rotations of a series of natural sugars.³

Substance.	Initial [α] _D .	Final [α] _D .
<i>d</i> -Glucose	105.2	52.6
<i>d</i> -Fructose	-104.0	-92.0
Galactose	117.5	80.4
Lactose	82.9	52.5
Maltose anhydride	118.7	137.0
Arabinose	156.6	104.5
Xylose	78.6	19.2
Rhamnose	-8.0	+9.4
Fucose	-112.0	-77.0

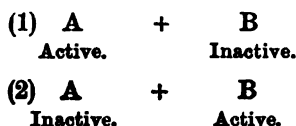
¹ *Zeit. phys. Chem.*, 1890, 6, 58; 1892, 9, 230.

² *Walden, Ber.*, 1897, 30, 2889.

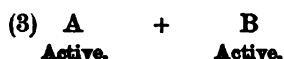
³ *Farcus and Tollens, Annalen*, 1890, 257, 160.

The change, which frequently takes several hours to complete, may be hastened by boiling the solution, or by adding certain reagents, such as ammonia or other alkali. It is clearly indicative of an alteration in the structure or configuration of the molecule. It is a subject of the greatest possible interest and is more fully discussed in the chapter on sugars (p. 380).

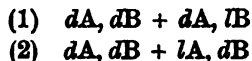
Optical Superposition. According to van't Hoff the optical effect of each asymmetric group is retained independently of the other asymmetric groups present in the compound, so that the total effect is the sum of the activities of all the asymmetric groups. This relation has been termed by Guye and Gautier¹ *optical superposition*. It has been experimentally tested by Guye and by Walden² in the following way, which on reflection will be seen to afford no proof of van't Hoff's proposition. Suppose the rotation of an ester, composed of an active alcohol A and an inactive acid B, is known, and also that of a second ester, composed of the inactive variety of the same alcohol A with one of the active acids of B, the two compounds will be represented as follows:



On summation of the results the inactive alcohol and acid cancel and leave



In other words, if two liquids (1) and (2) are mixed, the observed rotation will be due to the compound of active alcohol A with active acid B. The problem may be viewed in another way: (1) is a mixture of two esters, namely, active alcohol, which we will suppose to be the dextro-enantiomorph, with *d*- and *l*-acid, and (2) is also an assumed mixture of *d*-acid with *d*- and *l*-alcohol:



Now adding the two specific rotations is equivalent to mixing equal quantities of the two liquids. The compounds *dA*, *lB* and *lA*, *dB* are strictly enantiomorphous according to the theory, and will produce inactivity, leaving the active compound *dA* *dB*, which

¹ *Compt. rend.*, 1894, 116, 740, 952.

² *Zeit. phys. Chem.*, 1895, 17, 721.

comprises half of each original mixture (1) and (2), so that the combined effect gives the rotation dA, dB , that is, the sum of the rotations (1) and (2).

The following observations of Walden confirm the above theoretical deduction :

	L. i.	i. l.	L. l.	Calculated.
Amyl lactate	-6.88	+2.64	-8.98	-8.74
Amyl mandelate	-96.46	+2.76	-94.02	-98.70
Amyl malate	-9.92	+3.50	-6.88	-6.42
	d. i.		d. l.	
Amyl phenylchloracetate	+23.81	+8.23	+26.79	+26.54
Amyl chlorosuccinate	+21.56	+3.75	+25.15	+25.31
Amyl tartrate	+14.10	+3.87	+17.78	+17.47

It is clear that the result does not touch the question of the optical value of a particular group. In point of fact there is very definite evidence that the optical activity of a group is determined by its environment in the molecule and has no fixed value.¹

Rosanoff has deduced this from Walden's own observations. If the configurations of the asymmetric groups in *l*-amyl *d*-tartrate $[M]_D = +50.66^\circ$ and *l*-amyl *l*-tartrate $[M]_D = -31.12^\circ$ do not influence one another's rotation, the two esters should show the same differences in regard to the rotation of *l*-amyl mesotartrate, which Walden found to be $[M]_D = +18.88^\circ$, but the differences are far from being identical. Van't Hoff's assumption of optical superposition cannot therefore be sustained.

Theory of Guye and Crum Brown. Assuming optical activity to be a function of the asymmetry of the molecule, we are still ignorant of any direct connection between the two whereby the magnitude of the rotation may be measured in terms of the dimensions of the radicals composing the asymmetric molecule. Crum Brown² suggested that if each of the radicals possesses a function K which determines its rotation, the differences between these functions will give the rotation of the molecule. He concluded from experimental evidence that the function increases with the size of the radical. Guye³ has approached the subject from a similar, but broader, stand-

¹ Rosanoff, *J. Amer. Chem. Soc.*, 1906, 28, 528.

² *Proc. Roy. Soc. Edinb.*, 1890, 17, 181.

³ *Compt. rend.*, 1890, 110, 714; 1891, 111, 745; 1892, 114, 478; 1893, 116, 1133, 1378, 1451, 1454; 1894, 119, 906; 1895, 120, 167, 452, 682, 1274, &c.

point. The amount of asymmetry is determined by the displacement of the centre of gravity of the regular tetrahedron from its six planes of symmetry. The six values are measured by the distances of the six perpendiculars drawn from the centre of gravity to these six planes of the regular tetrahedron, and when multiplied together form what he terms the *product of asymmetry*. If $d_1 \dots d_6$ denote these distances, the product of asymmetry P is given by the expression :

$$P = d_1 \times d_2 \times d_3 \times d_4 \times d_5 \times d_6.$$

As a first approximation Guye assumed the tetrahedron to be regular, and estimated the values of $d_1 \dots d_6$ from the difference of the masses m_1, m_2, m_3, m_4 of the four radicals located at the summits. If $m_1 > m_2 > m_3 > m_4$ represent the order of magnitude of the masses the above expression becomes :

$$P = \frac{(m_1 - m_2)(m_1 - m_3)(m_1 - m_4)(m_2 - m_3)(m_2 - m_4)(m_3 - m_4)}{(m_1 + m_2 + m_3 + m_4)^6}.$$

This expression satisfies the following essential conditions, that if two groups are identical it equals zero, that is, the substance becomes inactive ; also, if two groups are interchanged, it becomes negative, which signifies a change of sign, that is, the formation of the enantiomorph. The results of the above expression may be stated as follows :

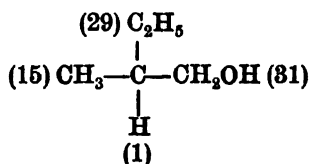
1. If the masses of any two radicals become equal, $P = 0$, that is, optical activity will vanish.

2. If m_1 increases or m_4 diminishes in value, P increases, and consequently the rotation will rise. Other relative changes will produce a rise or fall in rotation.

3. If there is a change of sign of 1, 3, or 5 of the factors, it will be followed by a change of sign of P . For example, when m_2 becomes greater than m_1 , the first factor becomes negative, and the compound, which we may suppose was originally dextro-rotatory, now becomes laevo-rotatory, the amount depending on the differences between the masses of the groups in question.

To test his theory, Guye compared the rotatory power of forty-three compounds derived from active amyl alcohol.

Active amyl alcohol has the formula :

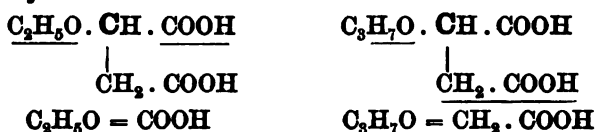


in which the masses of the radicals are in the order CH_2OH (81) > C_2H_5 (29) > CH_3 (15) > H (1). On increasing the mass (m_1) of the carbinol radical (R) there should be a corresponding increase in rotatory power. The following are some of the numbers obtained: ¹

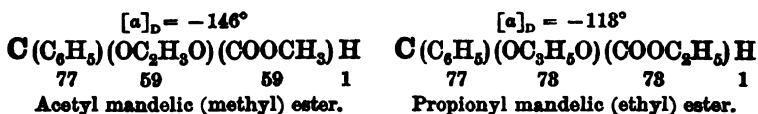
R.	m_1 .	Rotation.
CH_3CN	40	1° 16'
CH_2SH	47	1° 7'
CH_2Cl	49.5	1° 6'
$\text{CH}_2 \cdot \text{CO}_2\text{H}$	59	3° 20'
CH_2Br	94	4° 24'
CH_2I	142	8° 20'

The numbers agree well with the theory. Nevertheless the hypothesis in its original simplicity has not been supported by the results of subsequent research. Guye himself soon discovered that two different groups of equal mass did not destroy optical activity.

If active amyl alcohol is oxidised to the aldehyde, there are present in the molecule an ethyl ($\text{C}_2\text{H}_5 = 29$) and an aldehyde group ($\text{CHO} = 29$), both of which represent equal masses, yet the compound is active. Purdie ² has shown the same thing in the case of ethoxy- and propoxy-succinic acids.



and Walden has produced many similar examples, thus:



Walden ³ has subjected the theory to a still more searching criticism. He found that the acyl derivatives of the malic esters have a nearly equal rotation irrespective of the mass of the acid radical.

Acyl radical in dimethyl malate.	$[\alpha]_D$.
$\text{CH}_3\text{BrCO} = 122$	-22.40°
$\text{C}_2\text{H}_5\text{CO} = 85$	-22.39
$\text{CH}_2\text{ClCO} = 77.5$	-22.30
$\text{C}_2\text{H}_5\text{CO} = 71$	-22.40

¹ *Ann. Chim. Phys.*, 1893 (6), 25, 146.

² *Trans. Chem. Soc.*, 1895, 67, 946.

³ *Zeit. phys. Chem.*, 1894, 15, 688; 1895, 17, 245, 705.

The mono-halogen derivatives of the succinic esters, on the other hand, have a nearly equal dextro-rotatory activity irrespective of the alcohol radical. Walden finds that the following two substances, with groups of nearly equal masses, have nearly equal *but opposite* rotatory power:

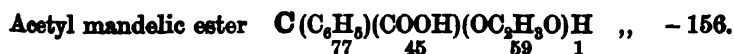
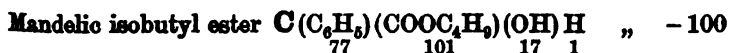
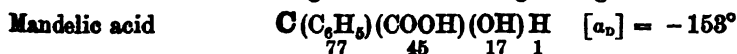
n-butyryl malic diisobutyl ester

$$m_1 = 115, m_2 = 101, m_3 = 87, [\alpha]_D = -26.68^\circ,$$

bromosuccinic diisobutyl ester

$$m_1 = 115, m_2 = 101, m_3 = 80, [\alpha]_D = +23.56^\circ.$$

Equality of the masses does not therefore produce inactivity, nor does inequality necessarily cause a change of rotation. Just as little does a reversal in the masses give rise to a change of sign.



REFERENCES

See end of Chapter III.

CHAPTER III

STEREOCHEMISTRY OF UNSATURATED AND CYCLIC COMPOUNDS (*GEOMETRICAL ISOMERISM*)

A FORM of isomerism which cannot be explained by ordinary structural relations, nor yet by molecular asymmetry, has long been observed among the unsaturated compounds of the ethylene series.

The earliest example is that of maleic and fumaric acid, both unsaturated dibasic acids of the formula $C_2H_2.(CO_2H)_2$. They are obtained from malic acid by distillation, when maleic acid in the form of its anhydride sublimes, whilst fumaric acid remains in the retort.

Fumaric acid sublimes at 200° without melting, is but slightly soluble in water, and crystallizes in needles; maleic acid melts at 180° , dissolves readily in water, crystallizes in rhombic prisms, and forms an anhydride at a temperature a little above its melting-point. The close similarity in structure follows from the fact that they both

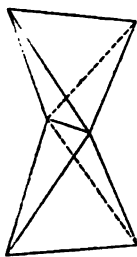


FIG. 10.

yield succinic acid on reduction, both regenerate malic acid on heating in a closed vessel with water, and each can be readily transformed into the other by means which will be presently described. The kind of isomerism was foretold by van't Hoff in *La Chimie dans l'Espace*, published in 1877. The importance of the theory then advanced has been brought into prominence by the experimental researches of J. Wislicenus, which were embodied in a brochure bearing the title *Die Lagerung der Atome im Raume*, and published in 1887. Van't

Hoff's conception of a simple unsaturated compound like ethylene is that of two regular tetrahedra united by a common edge with the four remaining summits occupied by hydrogen.

The same idea is presented by the four-bond carbon models by supposing the carbon atoms to be united by two pairs of bonds, and the remaining two pairs to be linked to hydrogen atoms.

If the bonds diverge at equal angles from the central carbon atom,

and retain their positions when the carbon atoms are doubly linked, the space arrangement of ethylene, viewed in perspective, will appear as in Fig. 11.

It follows from this space conception that the hydrogen atoms lie in one plane, and at the same time the free rotation of the carbon atoms is suspended, that is, the hydrogen atoms are fixed. If now the hydrogen atoms are replaced by two pairs of unlike groups *ab*, *ab*, or by groups *ab*, *ac* or *ab*, *cd*, the system will offer possibilities of space isomerism. By interchanging one pair of groups, which may be conveniently represented by projection formulae, the following pairs of isomers will be formed :

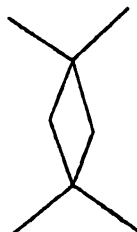
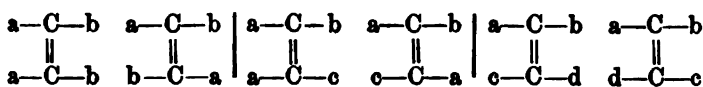


FIG. 11.



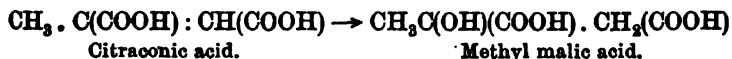
Fumaric and maleic acid will have the following space formulae :



Since the two pairs of groups lie in one plane, asymmetry is excluded, and with it both optical activity and enantiomorphous crystalline structure.

Le Bel's conception differs in a fundamental point from van't Hoff's. It neither assumes the tetrahedral grouping of van't Hoff nor the spatial distribution of four carbon bonds, so that it is left undecided whether the two pairs of groups attached to the carbon atoms lie in the same or in different planes ; in other words, it does not wholly exclude asymmetry, and isomerism may manifest itself by optical activity.

The few cases of supposed activity of ethylene derivatives have been traced to errors of observation. The activity of a solution of citraconic acid¹ produced by the growth of fungi was found to arise from the formation of methyl malic acid, probably by the activity first of water and then of the organism.



Citraconic acid.

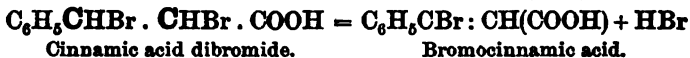
Methyl malic acid.

The supposed activity of styrene $\text{C}_6\text{H}_5\text{CH}:\text{CH}_2$ and of chlorofumaric and chloromaleic acid $\text{CO}_2\text{H} \cdot \text{CCl} : \text{CH} \cdot \text{CO}_2\text{H}$ ² belong to the

¹ Le Bel, *Bull. Soc. Chim.*, 1894 (8), 11, 292.

² Perkin, *Trans. Chem. Soc.*, 1888, 58, 695.

same category of inaccurate observations. It is significant in this connection that among the many unsaturated compounds found in nature, such as oleic, fumaric, coumaric, coumarinic, piperic acid, &c., not one is active. Even unsaturated compounds derived from active substances, like fumaric and maleic from active malic acid, bromocinnamic acid from active cinnamic acid dibromide, &c., are inactive :



Although all the facts support van't Hoff's theory which disposes of asymmetry in ethylene derivatives, it should be pointed out that where two ethylene linkages occur of the form Cab : C : Ced, asymmetry is possible, for the two pairs of groups now lie in planes at right angles to one another (Fig. 12).¹

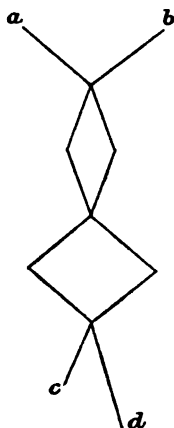


FIG. 12.

Such substances should exist in enantiomorphous forms and exhibit optical activity, but as they are difficult to prepare, experimental confirmation is still wanting. By a simple extension of the theory to trebly linked carbon atoms, a compound like acetylene would be represented by two tetrahedra with two faces in contact, or by a pair of carbon models attached by three bonds of each.

It is clear that a spatial arrangement of this character offers no possibility of space isomerism, a prevision which is fully attested by experience.

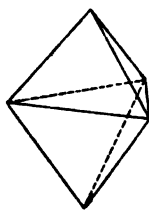


FIG. 13.

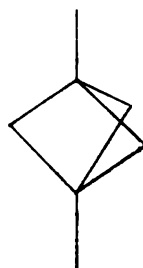


FIG. 14.

Properties of the Isomers. The theory of van't Hoff propounds a condition of things which bears a much closer resemblance to our

¹ See Perkin and Pope, *Proc. Chem. Soc.*, 1906, 22, 107, and Markwald and Meth, *Ber.*, 1906, 39, 1171, 2085.

conception of structural than of the optical isomerism. In fumaric and maleic acid the molecular dimensions and attractions are obviously different, and isomerism might therefore be expected to manifest itself by such properties as distinguish structural isomers. This view is confirmed by experience. The isomers differ in crystalline form, solubility, density, melting- and boiling-point, conductivity, or affinity constant; also in stability, which shows itself in chemical behaviour and heat of combustion; finally, in molecular dimensions, which determine certain aspects of chemical activity known as *steric hindrance* (p. 224). The spatial relations of the compounds not depending on structural differences, which distinguish them from structural isomers, are manifested by the ease with which they undergo mutual conversion on heating or by the action of reagents, recalling, in this respect, the process of racemisation or optical inversion.

Geometrical Isomers. In order to distinguish this kind of isomerism from that of optical isomers, on the one hand, and of structural isomers, on the other, the term *geometrical isomerism* has been introduced. It constitutes a special case of stereoisomerism. Among the characteristic groups which exhibit geometrical isomerism are the following:¹

Dimethylethylene	$\text{CH}_3 \cdot \text{CH} : \text{CH} \cdot \text{CH}_3$
Stilbene	$\text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH} \cdot \text{C}_6\text{H}_5$
Dibromoethylene	$\text{BrCH} : \text{CHBr}$
Diiodoethylene	$\text{ICH} : \text{CHI}$
α -Chlorobutylene	$\text{CH}_3 \cdot \text{CH} : \text{CCl} \cdot \text{CH}_3$
α -Bromobutylene	$\text{CH}_3 \cdot \text{CH} : \text{CBr} \cdot \text{CH}_3$
Chlorostilbene	$\text{C}_6\text{H}_5 \cdot \text{CH} : \text{CCl} \cdot \text{C}_6\text{H}_5$
Tolanedichloride	$\text{C}_6\text{H}_5\text{CCl} : \text{CClC}_6\text{H}_5$
Tolanedibromide	$\text{C}_6\text{H}_5\text{CBr} : \text{CBrC}_6\text{H}_5$
Diiodostyrene	$\text{C}_6\text{H}_5\text{Cl} : \text{CHI}$
<i>o</i> - and <i>p</i> -Dinitrostilbene	$(\text{NO}_2)\text{C}_6\text{H}_4\text{CH} : \text{CHC}_6\text{H}_4(\text{NO}_2)$
ω -Nitrostyrene	$\text{C}_6\text{H}_5\text{CH} : \text{CH}(\text{NO}_2)$
α -Aminostilbene	$(\text{NH}_2)\text{C}_6\text{H}_4\text{CH} : \text{CHC}_6\text{H}_4(\text{NH}_2)$
Crotonic and Isocrotonic Acid	$\text{CH}_3 \cdot \text{CH} : \text{CH} \cdot \text{COOH}$
Tiglic and Angelic	$\text{CH}_3 \cdot \text{CH} : \text{C}(\text{CH}_3) \cdot \text{COOH}$
Gaidic and Hypogæic	$\text{C}_{13}\text{H}_{27}\text{CH} : \text{CH} \cdot \text{COOH}$
Oleic and Elaidic	$\text{C}_8\text{H}_{17}\text{CH} : \text{CH}(\text{CH}_2) \cdot \text{COOH}$
Erucic and Brassidic	$\text{C}_8\text{H}_{17}\text{CH} : \text{CH}(\text{CH}_2)_{11} \cdot \text{COOH}$
α -Chlorocrotonic	$\text{CH}_3 \cdot \text{CH} : \text{CCl} \cdot \text{COOH}$
β -Chlorocrotonic	$\text{CH}_3 \cdot \text{CCl} : \text{CH} \cdot \text{COOH}$

¹ A more complete list will be found in Werner's *Lehrbuch der Stereochemie*, p. 189.

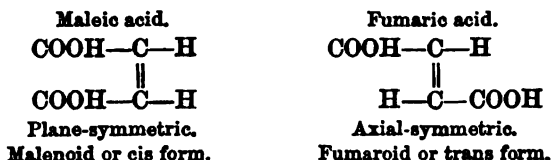
β -Bromoacrylic Acid	CHBr:CH. COOH
β -Iodoacrylic	CHI:CH. COOH
Cinnamic and Isocinnamic	$C_6H_5CH:CH. COOH$
Allo- and Isocallo-cinnamic ¹	" "
α -Chlorocinnamic	$C_6H_5CH:CCl. COOH$
α -Bromocinnamic	$C_6H_5CH:CBr. COOH$
β -Chlorocinnamic	$C_6H_5CCl:CH. COOH$
β -Bromocinnamic	$C_6H_5CBr:CH. COOH$
α -Methylcinnamic	$C_6H_5CH:C(CH_3). COOH$
α -Phenylcinnamic	$C_6H_5CH:C(C_6H_5). COOH$
Coumaric and Coumarinic	$(OH)C_6H_4CH:CH. COOH$
Fumaric and Maleic	$COOH. CH:CH. COOH$
Mesaconic and Citraconic	$COOH. CH:C(CH_3)COOH$
Phenylitaconic and phenyl- atonic Acid	$C_6H_5CH:C(CH_2COOH). COOH$

and numerous halogen, aryl, and alkyl derivatives of fumaric and maleic acid.

Determination of Configuration. Before discussing the methods which are used for determining the configuration of the geometrical isomers, the system of nomenclature must be briefly indicated. In the simplest case of two pairs of groups $abC:Cab$ the first of the two isomers



is distinguished by having the same groups on the same side of the molecule. It exhibits lateral symmetry, and is known as the *plane-symmetric*, or, more commonly, as the *cis* or *malenoid* form. The second isomer has its similar groups diagonally opposite, and is known as *axial-symmetric*, *trans* or *fumaroid* form. The terms malenoid and fumaroid have, of course, reference to maleic and fumaric acid, the configurations of which have been ascertained and correspond to the *cis* and *trans* forms:

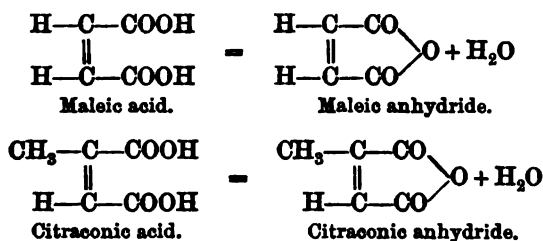


¹ The existence of four stereoisomers of cinnamic acid presents an anomaly for which an explanation has been put forward by Erlenmeyer and Arnold, *Annalen*, 1904, 337, 329.

Where only one pair of similar groups is present, the terms *cis* and *trans* apply to that pair; where all the groups are different the terms cannot be used, and the difference is indicated in some other way.

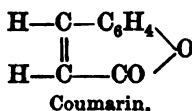
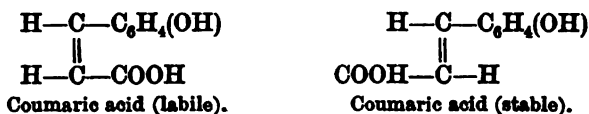
The general principle which underlies the methods used in determining configuration is one which has long lent itself to this kind of inquiry, namely, the interpretation of a chemical change as a mechanical process in which spatial relations of the original molecule persist in the new product, an assumption which, it may be said in passing, is not always supported by experience. The method has its limitations and must be used with caution, since such changes are not always simple and do not invariably proceed in what one is accustomed to call a normal fashion.

First Method. Formation of Cyclic Structures. Among the isomeric dibasic and hydroxy acids one member of the pair is usually found to yield an anhydride more readily than the other. Maleic and citraconic acids give anhydrides on heating, and are converted into the original acids when dissolved in water. This is taken as an indication of the proximity of the two carboxyl groups. Maleic and citraconic have therefore the *cis* configuration:

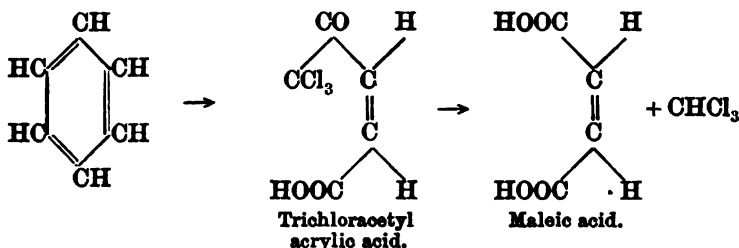


It is true that fumaric and mesaconic acid pass into anhydrides on heating, though less readily than the isomers, but the anhydrides are those of maleic and citraconic acids. That the above interpretation of the facts is correct follows from independent evidence afforded by the character of the stereoisomeric tartaric acids, which maleic and fumaric acid yield on oxidation, and which will be referred to presently (p. 114). The conversion of the two coumaric acids, $\text{OH} \cdot \text{C}_6\text{H}_4\text{CH}:\text{CH} \cdot \text{COOH}$, into lactones may be used in the same way to distinguish the *cis* from the *trans* isomer. One acid passes at once into the lactone, coumarin, when liberated from its salts by the addition of acid, whereas the second coumaric acid is much more stable and requires an active reagent like hydrobromic acid to effect the change. The lactone passes into the sodium salt on the addition

of sodium hydroxide, from which it is again liberated by acids, but if the strongly alkaline solution is boiled the second isomer is formed, which acids no longer precipitate as lactone. The first or labile acid will therefore have the hydroxyl and carboxyl in closest proximity.



The above examples will serve to illustrate the principle of the anhydride method for distinguishing geometrical isomers. The reverse of this process has been occasionally utilized for ascertaining configuration, but as the conversion of a ring into an open chain compound requires more drastic treatment than the former process, isomeric change may occur, and the results cannot be relied on with the same security. It is found, for example, that benzene and its derivatives usually give derivatives of maleic and not of fumaric acid. Benzene itself was converted by Kekulé¹ into trichloroacetyl acrylic acid, which breaks up in turn into maleic acid and chloroform:



Zincke² obtained dichloromaleic acid by the action of chlorine on *p*-aminophenol in alkaline solution. Derivatives of other ring compounds—furfurane, thiophene, and pyrrole—likewise yield derivatives of maleic acid.³

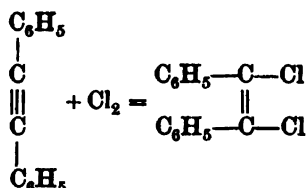
Second Method. Conversion of Acetylene into Ethylene Derivatives. When tolane $\text{C}_6\text{H}_5\text{C}:\text{CC}_6\text{H}_5$ combines with two

¹ *Annalen*, 1884, 223, 170.

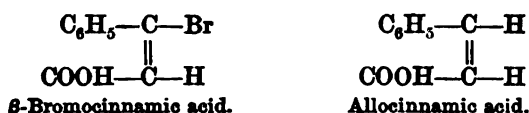
² *Ber.*, 1891, 24, 912.

³ Ciamician and Silber, *Ber.*, 1887, 20, 698, 2594; Ciamician and Angeli, *Ber.*, 1891, 24, 77, 1347.

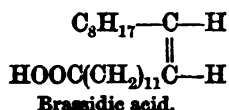
atoms of chlorine and passes into the dichloride $C_6H_5CCl:CClC_6H_5$, it might be supposed that the formation of a *cis* compound would produce the least disturbance in the molecular arrangement and would therefore be formed in the largest amount.



Consequently the tolane dichloride (*m. p.* 148°) obtained in this way may be regarded as the *cis* compound, whilst that obtained from the tolane tetrachloride by removal of chlorine (*m. p.* 68°) will represent the *trans* configuration. This principle, which was laid down by J. Wislicenus,¹ has been applied in a variety of cases. β -Bromocinnamic acid, obtained by the addition of hydrogen bromide to phenylpropionic acid, and its reduction product, allocinnamic acid, must have the following configuration :



Behenic acid $C_{19}H_{39}C:C.CO_2H$ gives on reduction brassidic and not erucic acid, and has the configuration :

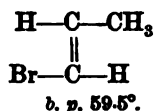
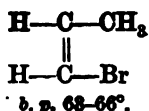


In these cases the accuracy of the conclusions cannot be supported by independent proof. It is otherwise with acetylene-dicarboxylic acid $COOH.C:C.CO_2H$, for the configuration of the additive compounds with bromine are known, and the product, which, according to the above argument, should consist mainly of dibromomaleic acid, contains, even under the most favourable conditions, a large proportion of dibromofumaric acid. The presence of the *trans* isomer was ascribed by Wislicenus to a secondary process, brought about by the action of bromine or hydrogen bromide on bromomaleic acid, but the explanation has been rendered untenable by Michael,² and the method has consequently lost something of its value. The reverse

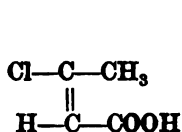
¹ *Die räumliche Anordnung der Atome*, p. 24.

² *J. prakt. Chem.*, 1892, 46, 210.

process of converting an ethylene into an acetylene derivative has also been proposed by Wislicenus, but appears to be open to the same disadvantage as the former one. Bromopropylene (*b. p.* 68–66°) is more slowly decomposed by alcoholic potash than its isomer (*b. p.* 59·5°), and the former is therefore assumed to have the hydrogen and bromine atoms in the *trans* position, whilst the latter represents the *cis* compound.



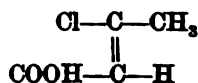
The configurations of the isomeric bromobutylenes have been determined in the same way. Chlorocrotonic acid is converted by potassium hydroxide into tetrolic acid at a lower temperature than chloroisocrotonic acid.



Chlorocrotonic acid.



Tetrolic acid.



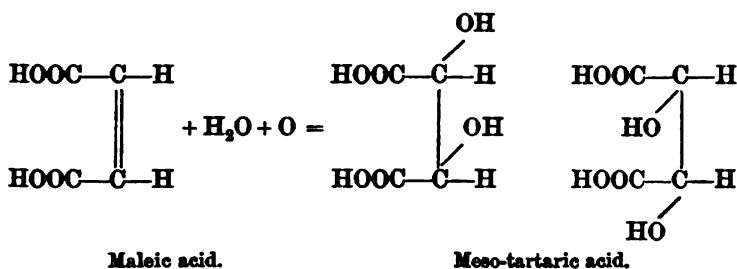
Chloroisocrotonic acid.

On the other hand, dibromofumaric ester is more easily transformed by zinc into acetylene dicarboxylic ester than its isomer, and the same is true of bromo- and chloro-fumaric acid.

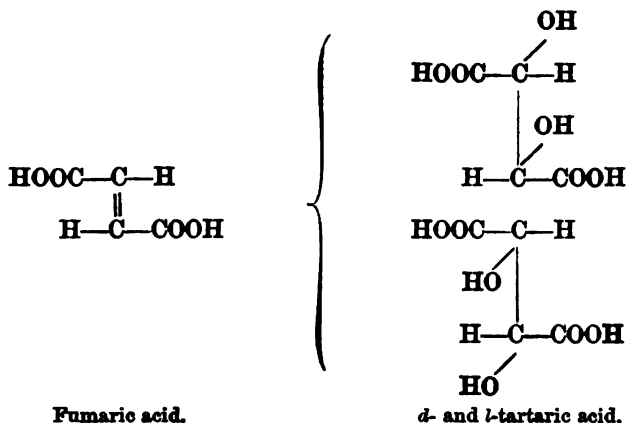
Third Method. Conversion of Ethylene Derivatives into Saturated Compounds. The method is perhaps best explained by taking, by way of illustration, an actual experiment. It has been found that when maleic and fumaric acid are oxidized with potassium permanganate, they take up two hydroxyl groups and yield inactive tartaric acids, but whereas maleic acid gives the *meso*-acid, fumaric acid yields *racemic* acid.¹ This result agrees precisely with the configuration of the two geometrical isomers ascertained by the first method. The mechanism of the change will be evident from the following considerations. Assuming, in the case of maleic acid, that the carboxyl groups and hydrogen atoms have the *cis* configuration, it follows that if either link of the double bond is broken, by the addition of hydroxyl groups, the same product must

¹ Kekulé and Anschütz, *Ber.*, 1880, 13, 2150; 1881, 14, 718.

result, namely, meso-tartaric acid, in which the two halves of the molecule stand in the relation of object and image.



If fumaric acid is oxidized the effect is otherwise, for the trans configuration will permit of the hydroxyl groups occupying two different positions according to which of the ethylene bonds is ruptured.



Now these two configurations stand in the relation of dextro and laevo tartaric acid, and, since they must be formed in equal quantity, racemic acid results (p. 72).

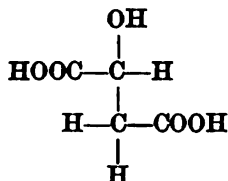
It is a curious fact that the dibromosuccinic acid which is obtained by the action of bromine on fumaric acid yields meso-tartaric and not racemic acid when the bromine is replaced by hydroxyl. The course of a reaction involving the use of bromine is, however, subject to influences which may produce abnormal results, for bromine appears to form trans additive compounds by preference, (p. 121), in addition to which it has a tendency to generate the more stable form (fumaric acid).

The reversal of the process just described, that is, the conversion

of asymmetric (meso and racemic) into ethylene compounds may be reckoned among the methods for ascertaining configuration, provided that the configuration of the original stereoisomers is known and the reaction proceeds in a normal fashion. The meso compound should yield the *cis* derivative and the racemic compound the *trans*. Experiment in this direction has not been attended with any great success. The removal of hydrogen bromide from the meso and racemic dibromosuccinic acids yields chiefly bromofumaric acid in both cases.

If the saturated compound is not of the asymmetric type, but is one like toluene tetrachloride $C_6H_5CCl_2 \cdot CCl_2C_6H_5$, which, by the action of zinc, can be converted into the unsaturated dichloride $C_6H_5CCl:CClC_6H_5$, the configuration of the product depends as before on that of the original substance. But there is no direct method for ascertaining the configuration of the original substance, and an entirely new problem is introduced.

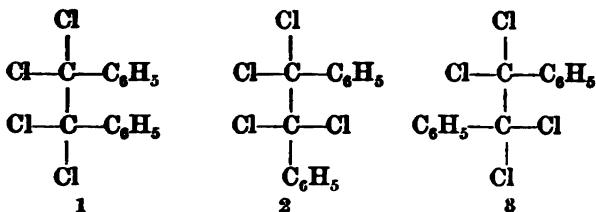
Are the Atoms attached to singly linked Carbon fixed? Do the different atoms or groups in a saturated compound of singly linked carbon atoms assume a fixed configuration relatively to one another, or are they in a state of oscillatory motion or rotation round the singly linked carbon? If, as Wislicenus and others suppose, the former is the case, and that the groups arrange themselves in positions of greatest stability, the difficulty of fixing these positions has still to be solved. Wislicenus proceeds in the following fashion: as fumaric acid is formed from malic acid at a temperature of $140-150^\circ$, whereas the anhydride of maleic acid only appears at a much higher temperature, he concludes that the favoured or more stable configuration of malic acid is represented by the following space formula:



The hydrogen atom and hydroxyl group occupy *cis* positions, since in forming fumaric acid they are removed together. As the effect of heat is to counteract chemical attraction, rise of temperature may alter the original conditions and the two carboxyls may swing round into *cis* positions, giving rise to the anhydride. An

attempt has been made to test the principle quantitatively in the following way:¹

Suppose in tolane tetrachloride the three configurations in which two chlorine atoms occupy *cis* positions to exist side by side in equal amounts, or, in other words, to offer no favoured configuration, a condition which might be supposed to obtain at a high temperature,



the removal of two atoms of chlorine by zinc would give only two tolane dichlorides, since 2 and 3 generate the same product.



It therefore follows that under conditions wherein all three configurations are equally stable, one-third of the *cis* form along with two-thirds of the *trans* isomer will be produced. Under conditions in which one of the three forms alone can exist, either the *cis* or *trans* form, but not both, would appear.

The first condition is fulfilled at 80°, and only one-third of this *cis* compound is formed; at lower temperatures the *trans* form predominates to the extent of considerably more than two-thirds. The question of fixity of configuration of saturated compounds is discussed more fully on p. 133.

Geometrical Inversion. A passing reference has been made to the mutual conversion of geometrical isomers or *geometrical inversion* and the resemblance which it bears to the process of racemisation or optical inversion. *Trans* formations of this character, produced both by physical and chemical agencies, were first observed with fumaric and maleic acid. It has already been stated that fumaric acid is converted into the anhydride of maleic acid on heating, and the same

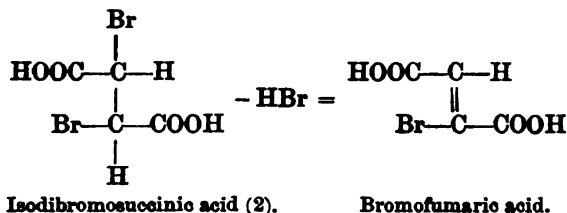
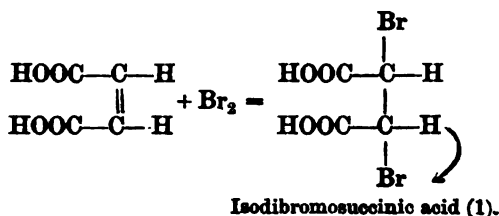
¹ Blank, *Annalen*, 1888, 248, 27.

result is obtained with many of its derivatives; maleic chloride passes into fumaric chloride on standing; the methyl ester of β -bromocinnamic acid (*m. p.* 147°) is converted into the isomer (*m. p.* 159°) on distillation; angelic acid passes into tiglic acid on heating for several hours. In many cases only one product results; in others, the process is reversible, for the same mixture of isomers is obtained whichever compound forms the starting-point. In a few cases light produces geometrical inversion. Paal and Schulze¹ found that sunlight converts yellow trans dibenzoyl ethylene into the colourless cis form, and Wislicenus has shown that angelic acid dibromide under these conditions passes into tiglic acid dibromide. The solvent in the process of crystallization is known to effect the same thing. Iodoacrylic acid (*m. p.* 65°) is converted on recrystallization into the isomer (*m. p.* 139–140°). Turning now to chemical reagents, maleic acid is converted into fumaric acid on heating with water under pressure; but the most effective reagents are the halogens and halogen acids. A trace of bromine or iodine converts maleic ester into fumaric ester. The action of the halogens is usually promoted by sunlight; the change of citraconic acid dissolved in ether into mesaconic acid, by the addition of a few drops of a chloroform solution of bromine, is very rapid on exposure to bright sunlight, and is readily observed. Iodine has a similar action on yellow dibenzalsuccinic acid, which passes into the colourless modification. Hydrochloric, hydrobromic, and hydriodic acid convert maleic into fumaric acid; nitrous acid converts oleic into elaidic, and hypogaeic into gaidic acid; also nitric acid can be used for transforming citraconic into mesaconic acid. Finally, caustic alkalis convert maleinaminic acid, $\text{NH}_2\text{OC} \cdot \text{CH} : \text{CH} \cdot \text{COOH}$, into fumaric acid and citraconic into mesaconic acid.

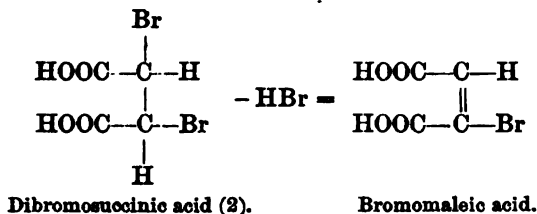
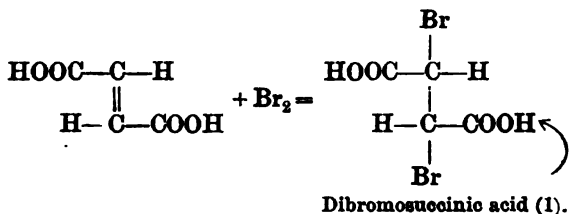
With few exceptions the conversion is complete, and probably follows the line of least resistance, that is, from the labile to the stable configuration. All these processes probably follow the law which governs isomeric change in general, and are cases of completed or incompleted reversible reactions accelerated by the intervention of a catalyst (see p. 205).

An insight into the mechanism of some of these changes is afforded by the following observations which are recorded by Wislicenus. Maleic acid forms with bromine the additive compound (meso) isodibromosuccinic acid, which, on boiling with water, loses hydrogen bromide and gives bromofumaric acid.

¹ *Ber.*, 1902, 35, 168.

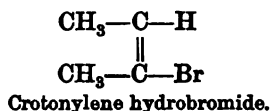
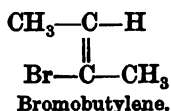


In order to explain the process it is necessary to suppose that one carbon group of isodibromosuccinic acid (1) rotates on an axis, formed by the bond joining the two carbon atoms, and in the direction of the arrow, until the hydrogen atom attached to the lower carbon comes opposite the bromine of the upper carbon group (isodibromosuccinic acid (2)), when hydrogen bromide is removed and bromofumaric acid results. Fumaric acid, in the same way, forms (racemic) dibromosuccinic acid, loses hydrogen bromide, and yields bromomaleic acid.

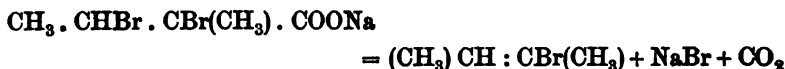


Similar observations have been made with tiglic and angelic acid, which are converted respectively into the corresponding dibromides, and finally, by inversion, into bromangelic and bromotiglic acid ; also

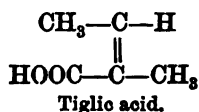
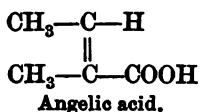
with erucic and brassidic acid, which form dichlorides, and then chloro-brassidic and chloroerucic acid. The process is not limited to acids. Stilbene (*m. p.* 124°) yields stilbene dibromide (*m. p.* 237°) and bromoisostilbene, whereas isostilbene gives isostilbene dibromide (*m. p.* 110°) and bromostilbene. The *cis* and *trans* butylenes pass through their respective dibromides by inversion into bromobutylene (*b. p.* 98.5°) and crotonylene hydrobromide (*b. p.* 85°).



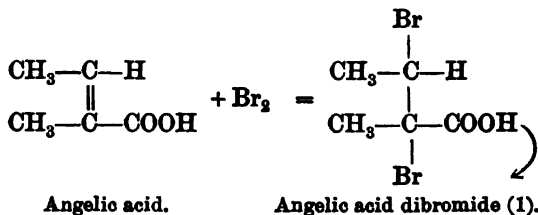
The relationship between the configurations of tiglic and angelic acids and the two bromobutylenes has been shown by Wislicenus in a very simple and suggestive way. When the dibromides of tiglic and angelic acid are boiled with sodium hydroxide, carbon dioxide and sodium bromide are removed and a bromobutylene results.



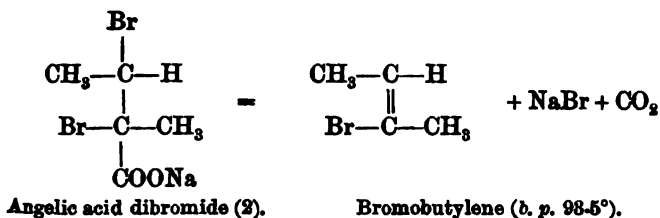
Angelica acid, according to the above interpretation, should give bromobutylene (*b. p.* 98.5°), and tiglic acid should yield the isomer. We will see how these results correspond with the principle just laid down. According to Wislicenus angelic and tiglic acids have the following formulae:



Angelica acid forms a dibromide which undergoes inversion.

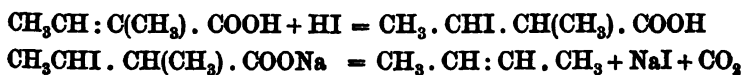


The sodium salt then brings about rotation into position (2), where the sodium atom of the lower carbon group is in the *cis* position to the bromine of the upper carbon.



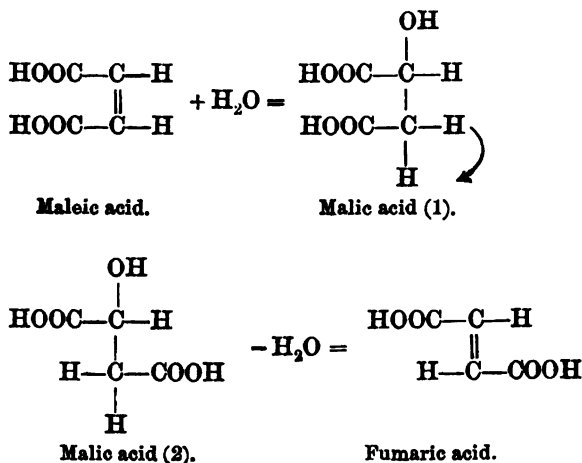
The isomeric crotonylene hydrobromide is obtained from tiglic acid in precisely the same manner.

The formation of the two butylenes from tiglic and angelic acid has been effected and their relation determined on similar lines. Briefly stated, the process consists in forming the addition compound of the acid with hydrogen iodide and boiling the latter with caustic soda solution.



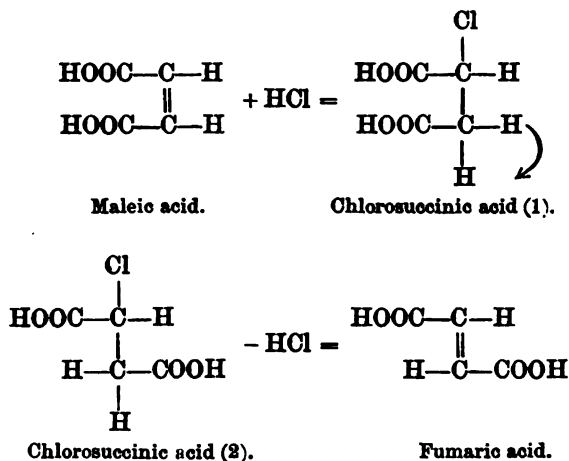
The two butylenes which boil at 1–1.5° and 2–2.7° respectively can be identified by means of their dibromides.

The mechanical conception which Wislicenus has so ingeniously applied to the action of bromine in causing geometrical inversion has not met with an equal measure of success in explaining other manifestations of the same phenomenon. The action of water in converting maleic into fumaric acid might be explained by the intermediate production of malic acid, followed by rotation into the favoured configuration and elimination of water.



This theory of the transformation cannot be sustained, for Skraup¹ failed to convert malic acid by heating it with water into fumaric acid under conditions in which geometrical inversion readily succeeds.

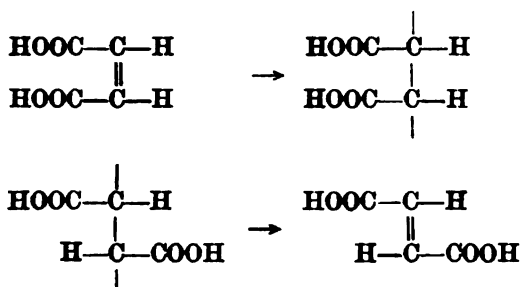
Traces of the halogen acids convert maleic acid into fumaric acid. Wislicenus explains the change in the usual way by the formation of an additive compound, followed by rotation into the stable configuration and the final separation of hydrogen halide.



The difficulty encountered in this assumption arises from the fact that the intermediate monohalogen succinic acids are actually stable at the temperature at which the conversion takes place. Anschütz has shown that whilst strong hydrochloric acid at 10°, and hydrobromic acid at 0°, convert maleic into fumaric acid, monochloro- and monobromo-succinic acid are perfectly stable at these temperatures, and exhibit no tendency to lose hydrogen chloride or bromide. The action of iodine in converting maleic into fumaric acid is explained as follows. Iodine is supposed to yield a diiodo additive compound of maleic acid, from which hydrogen iodide separates and reduces the iodofumaric acid to fumaric acid. In the conversion of maleic into fumaric acid by heat, the double bond connecting the carbon atoms in the former is loosened so as to permit of free rotation of the carbon atoms into the more stable configuration.

It follows that when the double linking occurs on cooling, fumaric acid is formed.

¹ *Monatsh.*, 1891, 12, 108.



The reader is reminded of the action of alkalis and of nitrous and nitric acid in effecting optical inversion, which, according to the theory of Wislicenus, would necessitate the formation of intermediate additive compounds with these substances. Still more striking are the facts discovered by Skraup of the partial inversion of metallic salts of maleic acid by precipitation of the metal by hydrogen sulphide. The same observer has also found that, although hydrogen sulphide and sulphur dioxide acting separately on a solution of maleic acid produce no effect, their united action causes partial inversion. In conclusion it should be mentioned that exposure to light alone is sufficient to cause inversion. It is clear from the examples given that the mechanical theory of Wislicenus cannot be indiscriminately applied and that in many cases it is either contrary to fact or manifestly improbable. A variety of attempts have been made to throw light on this complex change. Skraup suggests that an exothermic reaction, such as the combined action of hydrogen sulphide and sulphur dioxide in a solution of the isomer, or the incipient formation of an additive compound which may occur in certain cases, acts catalytically by setting up vibrations which he compares to the physical phenomenon of resonance or the chemical effect of an explosion wave. The theory possesses one convenient attribute. Like the old vibration theory of fermentation it stands beyond the reach of direct experimental disproof.

The same may be said of Werner's theory, which postulates the even distribution of affinity or valency over the surface of the carbon atom, which may take the form of a sphere. The four radicals of a saturated carbon atom occupy positions corresponding to the summits of a tetrahedron as the result of a tendency to neutralize most effectively their mutual attractions. In doubly linked carbon atoms the affinity which binds the pair of radicals to each of the two carbon atoms may be represented by two segments of a carbon sphere (unshaded in Fig. 15), the remainder, which is shaded in the

figure, being used for binding the two carbon atoms together. Of the latter, the segments corresponding to the more deeply shaded portions *a* do not prevent free rotation, which is entirely controlled by the mutual attractions of the smaller surfaces *b*. The latter act like elastic bands attached one on each side of the sphere, thereby keeping the atoms in position.

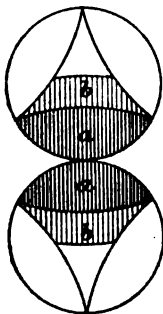


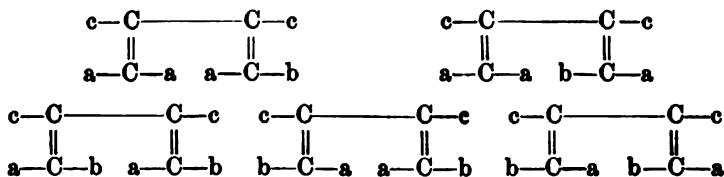
FIG. 15.

This small fraction of affinity is easily neutralized by rise of temperature or chemical action, and the spheres will then be free to revolve through 180° , that is, into the opposite configuration.

Geometrical inversion is clearly the result of a variety of different conditions at present imperfectly understood. The conditions which determine the formation of additive compounds—the basis of Wislicenus' hypothesis—furnish a problem which still awaits exhaustive treatment; so much at least may be said; the additive process is greatly modified by the nature of the groups attached to the unsaturated carbon atoms.

At present we must leave the subject of geometrical inversion without the embellishment of a theory which embraces all the phenomena.

Geometrical Isomers with more than one Ethylene Linkage. Few examples of isomers containing two ethylene linkages are known. Compounds of the formula $aaC:Cc.Cc:Cab$ may exist in two stereoisomeric forms, whilst in the case of $abC:Cc.Cc:Cab$ the number is increased to three.



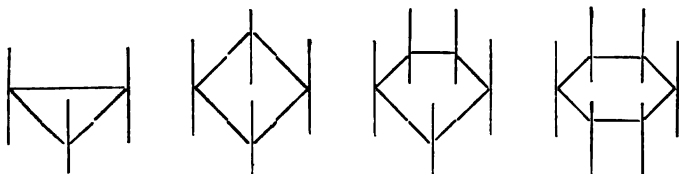
Stobbe¹ has obtained not only three isomeric dibenzalsuccinic acids of the formula $C_6H_5CH:C(COOH).C(COOH):CHC_6H_5$, but an additional anhydride which is formed by the action of light on the anhydride of one of the other three acids. The configuration of none of these compounds has been ascertained, and the existence of the fourth isomer remains unexplained.

¹ *Gesell. Naturforscher and Aerzte, München, 1899, 88.*

Stereoisomerism of Cyclic Compounds. A short account has already been given (p. 90) of the optical isomerism of cyclic compounds containing asymmetric carbon in the nucleus. The stereochemistry of this class of compounds must now be developed a little more fully.

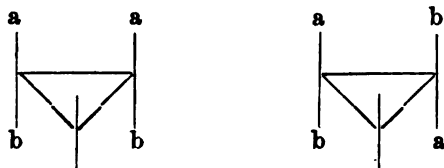
In his original pamphlet van't Hoff discussed the subject of the stereoisomerism of cyclic compounds, although the only example known at the time which fulfilled the necessary conditions was Baeyer's hydro- and isohydro-mellitic acids, $C_6H_6(COOH)_6$. Van't Hoff's conclusions have since been amply verified by the researches of Baeyer, Baumann and Fromm, Buchner, W. H. Perkin, jun., and others.

If the carbon atom is represented in the usual way with four bonds directed to the four corners of a tetrahedron, and then three or more carbon atoms be joined by single bonds in the form of a ring or closed chain, the arrangement drawn diagrammatically may be represented as follows; the pairs of available bonds, for the sake of simplicity, are rendered by vertical lines at right angles to the contour orbit of the ring, and the ring itself lies in a plane vertical to that of the paper and must be viewed as if in perspective, as previously explained (p. 91).



Each carbon atom, therefore, possesses two residual linkages, which may be joined to different pairs of atoms or groups. As the power of free rotation of the carbon atoms is suspended by the fact of their being linked in a ring, the space arrangement should bear some analogy to that of the doubly linked carbon atom and should manifest characteristics of cis-trans isomerism; in other words, the isomers should exhibit the differences in properties which distinguish compounds of the fumaric and maleic acid type.

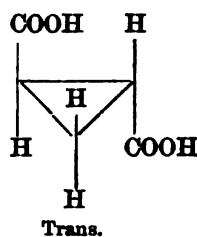
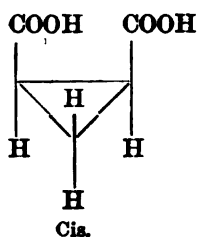
Thus, a derivative of trimethylene with two pairs of groups *a*, *b*, should possess the following configurations:



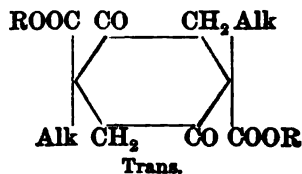
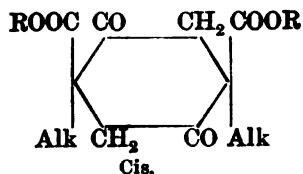
Examples of this kind of isomerism are now very numerous and embrace a variety of different groups of compounds. They include the dicarboxylic acids of cyclo-propane, -butane, -pentane, and -hexane. The isomers are distinguished as *cis* and *trans* for reasons to be presently discussed.

Name.	Melting-point.	
	Cis.	Trans.
1.2 Cyclopropane dicarboxylic acid	189°	175°
1.3 Cyclobutane " "	185-186	170-171
1.2 " " "	187-188	181
1.2 Cyclopentane " "	140	159-160
1.3 " " "	120-121.5	87-88.5
Hexahydrophthalic acid	192	215
Δ^4 Tetrahydrophthalic acid ¹	174	218
$\Delta^{3,5}$ Dihydrophthalic acid	178-175	210
Hexahydroisophthalic acid	161-163	118-120
Δ^4 Tetrahydroisophthalic acid	165	227
Hexahydroterephthalic acid	161-162	300
Δ^3 Tetrahydroterephthalic acid	150-155	about 200
$\Delta^{3,5}$ Dihydroterephthalic acid	—	—
Camphoric acid (p. 509)	188	170 (iso)
Caronic acid (p. 488)	174-175	212
Truxillic acid	$\alpha = 274$	$\gamma = 228$

Taking one example from the above list, the two cyclopropane dicarboxylic acids will appear as follows:



A series of dialkyl succino-succinic esters are known in isomeric forms², which probably have the following structure:



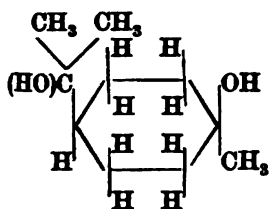
Dialkyl succino-succinic esters.

¹ The use of the symbol Δ is explained on p. 450.

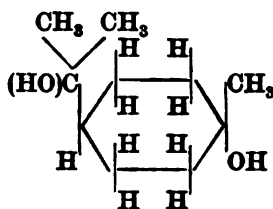
² Baeyer, *Ber.*, 1893, 26, 252.

Also a number of substances belonging to the terpene group :

	Cis.	Trans.
Terpin (anhydrous) (p. 477)	102-105°	156-158°
Dipentene dihydrochloride (p. 474)	25	50
Limonene nitrosochloride (p. 482)	103-104	105-106
Menthylamine	207-208	209-210



Cis. Terpin.



Trans. Terpin.

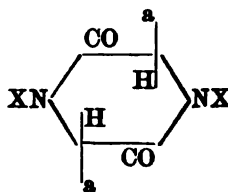
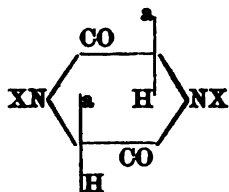
and a variety of cyclohexane derivatives.

	m. p.	m. p.
Quintol	139°	100-102°
Dimethyldiketo cyclohexane	98	115-117
1-4 Dibromo cyclohexane	118	liquid
Benzene hexachloride	310	157
Benzene hexabromide	258	212

Several of the alkaloids exist as cis and trans isomers.

	Cis.	Trans.
Tropine (p. 579)	61.3°	108°
Egonine (p. 584)	198	257
Cocaine (p. 584)	98	46-47

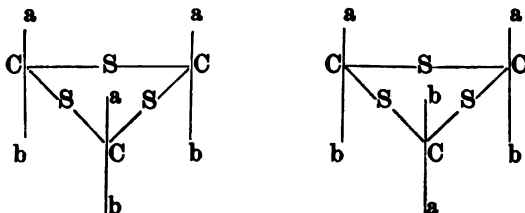
The heterocyclic compounds are represented by diketopiperazines of Bischoff¹ and Fischer² of the general formulae:



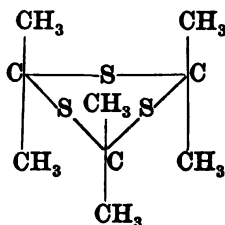
¹ Ber., 1892, 25, 2950.

² Ber. 1906, 39, 3981.

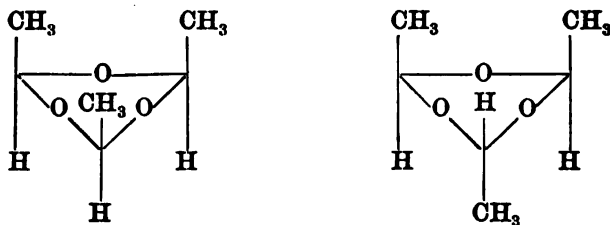
whilst a series of isomeric trithiomethylene derivatives have been obtained by Baumann and Fromm¹ by the polymerisation of thioaldehydes and thiaketones. They are substances which may be represented by the general formulae :



It is significant that when the groups *ab* are identical, as in trithioacetone derived from thiacetone, and when, according to the theory, isomerism is impossible, only one form is known.



It is probable that paraldehyde and metaldehyde belong to the same type of *cis-trans* isomerism.

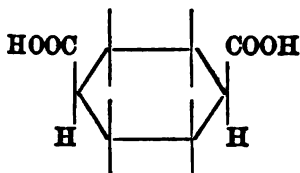


Determination of Configuration. The isomeric dibasic acids may generally be divided into a *cis* or malenoid and a *trans* or fumaroid type, exhibiting the distinctive characteristics of maleic and fumaric acid. The *cis* or malenoid form is distinguished by its greater solubility in water, its lower melting-point, its affinity constant (which is usually, though not invariably, higher), also by its anhydride formation (which is more readily effected than that of its isomer) and its conversion into the *trans* isomer by the aid of hydrochloric acid. The *trans* or fumaroid form is much less soluble in water; it has

¹ *Ber.*, 1891, 24, 1419.

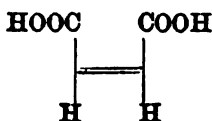
a higher melting-point, and occasionally yields an anhydride on heating with acetyl chloride, which, on more prolonged heating, passes into the anhydride of the *cis* form.

The following comparison between *cis* and *trans* hexahydrotetraphthalic acid and fumaric and maleic acid will illustrate the parallelism existing between the two pairs of compounds.



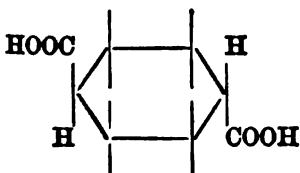
Cis Hexahydrotetraphthalic acid.

Crystallizes in large plates (m. p. 161-163°). Much more soluble in water than the *trans* form. Transformed into the *trans* form when heated with hydrochloric acid.



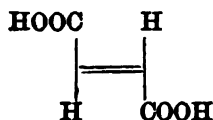
Maleic acid.

Crystallizes in large plates (m. p. 130°). Much more soluble in water than fumaric acid. Transformed into fumaric acid when heated with hydrochloric acid.



Trans Hexahydrotetraphthalic acid.

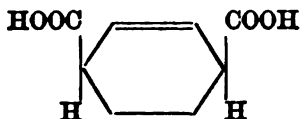
Crystallizes in short prisms, sublimes when heated, and melts at 300°. Forms no anhydride.



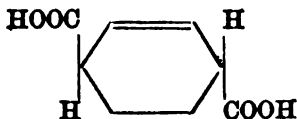
Fumaric acid.

Crystallizes in small prisms, sublimes at 300°. Forms the anhydride of maleic acid on heating.

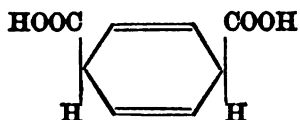
The partly saturated di- and tetra-hydrobenzene dicarboxylic acids also furnish examples of geometrical isomers and show similar differences in properties (see p. 126).



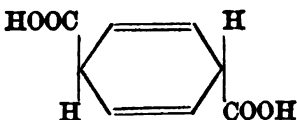
Cis Δ⁹ Tetrahydrotetraphthalic acid.



Trans Δ⁹ Tetrahydrotetraphthalic acid.



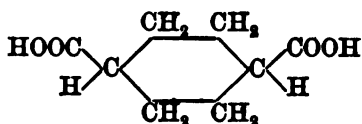
Cis Δ^{1,4} Dihydrotetraphthalic acid.



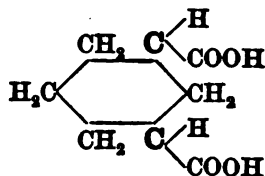
Trans Δ^{1,4} Dihydrotetraphthalic acid.

Thus in the case of the dibasic acids there is little difficulty in ascertaining the configuration of the isomers. In other cases the criteria are less satisfactory. It is generally assumed that the compound of higher melting-point corresponds to the *trans* form, but this distinction cannot be implicitly accepted. Occasionally the experience derived from steric hindrance (see p. 224) will give some information.

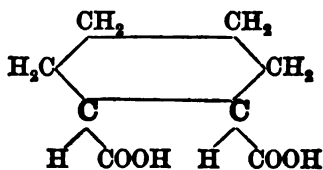
Absolute and Relative Asymmetry. From the list of dibasic acids on p. 126 it will be seen that the three hexahydrophthalic acids are represented by *cis* and *trans* isomers, but there is an important distinction between the *para* compound and the other two, for the latter contain asymmetric carbon atoms whilst the former does not. This is seen by reference to the space formulae.



Hexahydroterephthalic acid.

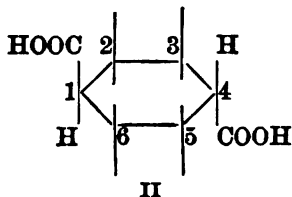
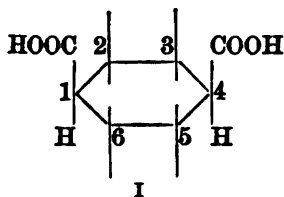


Hexahydroisophthalic acid.

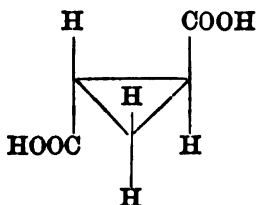
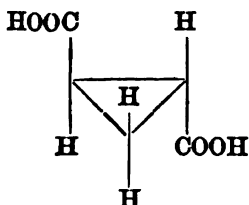


Hexahydrophthalic acid.

But there is a distinction between hexahydroterephthalic acid and an ordinary symmetrical open-chain compound, to which Baeyer has drawn attention. For if a person is represented as floating on his side in the orbit of the ring, with his face to the centre and his hands outstretched at right angles to the plane of the ring; further, supposing his feet to be at 1, and his head at 2, he will on reaching 4 in formula I (*cis* form) see carboxyl on his right and hydrogen on his left, whereas if he starts with head at 6 and feet at 1, he will see on arriving at 4 carboxyl on his left and hydrogen on his right. The same is true of formula II (*trans* form). The structure as a whole is therefore unsymmetrical, and to this Baeyer has given the name *relative asymmetry*.

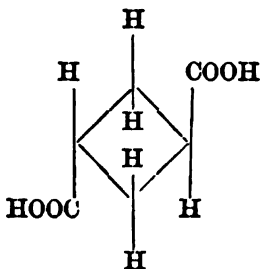
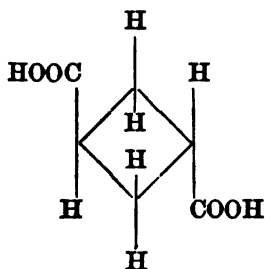


Hexahydro-phthalic and -isophthalic acids should therefore be separable into optical enantiomorphs, but not the hexahydroterephthalic acid. The resolution of hexahydrophthalic acid has in fact been accomplished by Werner and Conrad¹ (p. 92). The same principle is applicable to the other cyclic isomers. Thus 1.2 cyclopropane dicarboxylic acid contains two asymmetric carbon atoms and the two trans forms are non-superposable, and the same is true of 1.2 cyclobutane dicarboxylic acid, whereas cis and trans



Trans 1.2 Cyclopropane dicarboxylic acid.

1.3 cyclobutane dicarboxylic acids are examples of relative asymmetry, and each form is identical with its mirror-image. The conditions



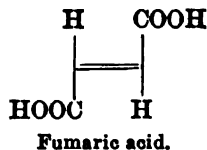
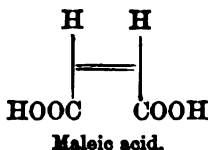
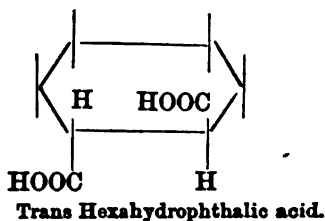
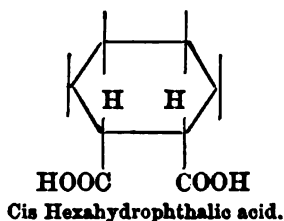
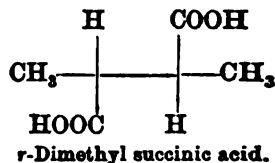
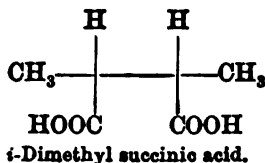
Trans 1.3 Cyclobutane dicarboxylic acid.

of asymmetry may be conveniently studied by means of the cardboard models described on p. 98.

Combined Optical and Geometrical Isomerism. The question now arises: which of the two geometrical isomers containing

¹ Ber. 1899, 32, 3046.

asymmetric carbon is inactive by internal, which by external compensation? A little reflection will furnish the answer, for the cyclic orthodibasic acids stand midway in configuration between the dialkyl succinic acids and the unsaturated acids of the maleic-fumaric type. The relationship will be evident from the following formulae:



The *cis* configuration represents the meso compound, the *trans*, the racemic form. This has been proved, as already stated, by Werner and Conrad, who succeeded in resolving the *trans* compound into its optical enantiomorphs (p. 92).

The correspondence between each pair of the three types of dibasic acids described above is not one of configuration only, for it is exhibited in a very striking fashion by a close resemblance in physical and chemical properties. The following scheme will make this clear.

i-Dimethyl succinic acid.

m. p. 120°. Readily forms an anhydride (*m. p.* 87°); more soluble in water than its isomer, into which it is converted by strong hydrochloric acid.

Cis Hexahydrophthalic acid.

m. p. 193°. Passes readily into the anhydride (*m. p.* 32°); is more soluble in water than its isomer, into which it is transformed by heating with strong hydrochloric acid.

r-Dimethyl succinic acid.

m. p. 192°. Forms an anhydride with acetyl chloride (*m. p.* 88°), which when heated forms the anhydride of the meso compound.

Trans Hexahydrophthalic acid.

m. p. 215°. Treated with acetyl chloride it forms an anhydride (*m. p.* 140°); when heated it is transformed into the *cis* anhydride.

Maleic acid.

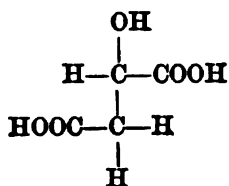
m. p. 130°. Readily forms an anhydride on heating; more soluble in water than its isomer, and is converted by hydrochloric acid into fumaric acid.

Fumaric acid.

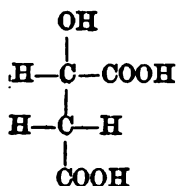
m. p. 286–287°. Sublimes at 200°; forms the anhydride of the *cis* form on continued heating or with acetyl chloride.

It will be seen that in all three cases the malenoid form has the lower melting-point, and is the more soluble and the less stable isomer.

Fixed Configuration of Open-chain Compounds. Several interesting questions arise out of the stereochemical relations subsisting between saturated and unsaturated open-chain compounds and the saturated or partly-saturated cyclic compounds, which, as we have seen, stand midway between them. For the latter exhibit many of the characteristic properties of geometrical isomers of the ethylene series, whilst they frequently resemble the open-chain compounds in their manifestation of optical activity. This dual character is seen concurrently where two similar asymmetric and nuclear carbon atoms adjoin one another as in the orthodibasic acids. The resemblance in certain physical and chemical properties between the *cis* and *trans* hexahydrophthalic acids and the two dimethyl succinic acids, on the one hand, and of fumaric and maleic acid, on the other, has been described, and its significance is unmistakable. It clearly indicates the fixed configuration of the groups in the dimethyl succinic acids, since they possess the distinguishing characteristics of geometrical isomers. This question has already been referred to on p. 116. According to Aberson¹ the third active malic acid found by Schmidt and Meyer in certain species of *Echeveria* can only be explained on the assumption of a fixed configuration of the radicals in these acids, to which Aberson attaches the following formulae:



Ordinary malic acid.



Aberson's acid.

Hantzsch² suggests that the two $\alpha\beta$ -dibromopropionic acids, $\text{CH}_2\text{Br} \cdot \text{CHBr} \cdot \text{COOH}$, of Linnemann, which are readily interconvertible, and the three α -phenyl hydrocinnamic acids,



¹ Ber., 1898, 31, 1432.

² Grundriss der Stereochemie, p. 99.

of von Miller are to be accounted for in the same manner. The conversion of geometrical isomers of the *cis-trans* type, like fumaric and maleic acid, into the same product on reduction (succinic acid) appears at first sight to contradict this view, but it is readily explained by supposing that singly linked carbon atoms will in the majority of cases assume, by free rotation, the most stable configuration, and consequently no second compound is formed. There appears to be no direct means of ascertaining this favoured configuration, and the various proposals which have been suggested partake more or less of a speculative character. A certain amount of information has been derived from the behaviour of the alkyl succinic acids. It is well known that the facility with which they pass into anhydrides increases with the number of alkyl groups present. Succinic acid itself demands a higher temperature for conversion into the anhydride than mono- and di-methyl succinic acid, whilst tetramethyl succinic acid, even in aqueous solution, passes spontaneously into the anhydride. This property of anhydridisation seems to change concurrently with conductivity. Whereas succinic acid has a dissociation constant, $K = 0.0068$, which is nearer to fumaric acid, $K = 0.09$, than to maleic, $K = 1.2$, the methyl succinic acids have the following constants¹:

	K
Monomethyl succinic acid	0.0085
<i>s</i> -Dimethyl succinic acid	0.0123 (<i>cis</i>), 0.0196 (<i>trans</i>)
Trimethyl succinic acid	0.0194
Tetramethyl succinic acid	0.0314

As it is usually found that the proximity of acid groups, such as the ortho-nitro substituted acids of the benzene series, increases the conductivity, it is fair to presume that the tendency in the methyl succinic acids is for the carboxyl groups to be driven into juxtaposition by increasing the number of methyl groups. The tendency of succinic acid will consequently be towards the *trans* configuration, that of tetramethyl succinic acid towards the *cis* configuration. It must be confessed that such a line of reasoning leads to no very satisfactory conclusion, but the subject is one of great interest and would repay further study.

¹ Walden, *Zeit. phys. Chem.*, 1891, 8, 438; Bone and Sprankling, *Trans. Chem. Soc.*, 1899, 75, 864; Bethmann, *Zeit. phys. Chem.*, 1890, 5, 404.

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CHAPTER IV

STEREOCHEMISTRY OF NITROGEN

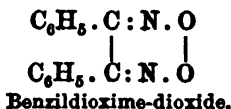
Historical. In 1888 Goldschmidt,¹ working under the direction of V. Meyer, discovered an isomer of benzildioxime. It was found on investigation that the two were structurally identical, and consequently stereoisomeric. This unexpected result opened out a new and, as it has since proved, remarkably fertile field of research in stereochemistry. The first, or α -benzildioxime, is obtained by digesting equivalent weights of benzil dissolved in alcohol and hydroxylamine hydrochloride on the water-bath. It melts at 237°.



The second, or β -compound, is prepared by heating an alcoholic solution of benzil with an excess of hydroxylamine hydrochloride in a sealed tube at 170°. It is colourless, like the first, but melts at 206–207°, and is more soluble in the ordinary solvents. In 1889 V. Meyer and Auwers² discovered a third, or γ -dioxime, which is obtained from the dioxide (see below) by reduction, and melts at 164–166°. Each substance has the normal molecular weight, and gives a parallel series of ethers and esters of the general formula :



Each is decomposed with hydrochloric acid into the original benzil and hydroxylamine, yields dibenzil on reduction, and a dioxide on oxidation³.



The α -compound is the least stable ; for, when heated with alcohol to 170°, or with water to 200°, it passes into the β -modification, and there are other ways of effecting the same result.⁴

¹ *Ber.*, 1888, 15, 1616, 2176.

² *Ber.*, 1889, 22, 705.

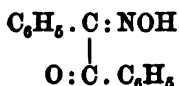
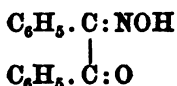
³ Koraef, *Ber.*, 1886, 19, 183.

⁴ Auwers, *Die Entwicklung der Stereochemie*, p. 88.

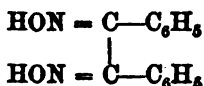
In 1888 V. Meyer and Auwers¹ obtained two isomeric benzil-monoximes; one (α) of melting-point 137–138°, was obtained by the action of free hydroxylamine on benzil in the cold alcoholic solution, and the other (γ) of melting-point 118–114°, by digesting an aqueous alcoholic solution of benzil with hydroxylamine hydrochloride on the water-bath. They are also structurally identical, and, like the dioximes, form a parallel series of alkyl and acyl derivatives. The first may be readily converted into the second by heating with alcohol to 100°, or by passing hydrochloric acid gas into the α -compound dissolved in a mixture of acetic acid and anhydride (Beckmann's method).

By the action of free hydroxylamine on the second or γ -monoxime, the γ -dioxime, referred to above, is obtained.

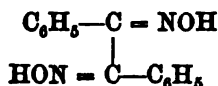
Theory of Meyer and Auwers. The theory proposed by V. Meyer and Auwers² to account for these cases of isomerism had reference to the linking of the carbon atoms. Different space arrangements of the molecule were produced by the carbon atoms becoming fixed, that is, losing their power of rotation, and so occupying a different relative position. The two monoximes were represented thus :



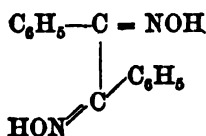
The three dioximes appeared as follows :



1



2



3

In formula 3 the two pair of groups are situated in two planes, at right angles.

Such a theory was contrary to van't Hoff's conception of stereoisomerism, which postulates no second form in singly linked carbon compounds unless the carbon group is asymmetrical; it was opposed to previous experience, and, in addition, there seemed no reason why the number of either monoximes or dioximes should be restricted to two in one case and three in the other. On the same principle it would be possible to construct two additional monoximes and a fourth dioxime.

¹ Ber., 1888, 21, 784, 8510.

² Ber., 1890, 23, 594.

When, therefore, isomeric *p*-chlorobenzophenoneoximes,



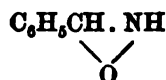
and other unsymmetrical ketoximes appeared without the requisite pair of singly linked carbon atoms, the theory could no longer be upheld, and it was forthwith abandoned.

About this time Beckmann¹ announced the discovery of a second oxime of benzaldehyde.

The ordinary or α -compound (*m. p.* 85°) is obtained by adding hydroxylamine hydrochloride gradually to a mixture of benzaldehyde and strong caustic soda solution, from which, after passing in carbon dioxide, the oxime is extracted with ether²; the β -compound is obtained in the form of the hydrochloride by passing hydrogen chloride into an ethereal solution of the α -compound. The addition of soda liberates the β -compound, which melts at 180°, and readily reverts to the α -form on standing. Beckmann³ represented the two forms by different structural formulae on the following grounds:

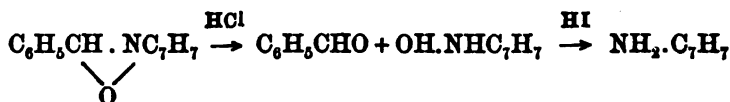
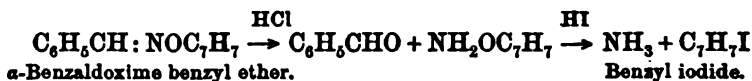


α -Benzaldoxime.



β -Benzaldoxime.

Both compounds form benzyl ethers, which decompose with hydrochloric acid into benzaldehyde and benzylhydroxylamine; but, whereas the benzylhydroxylamine from the α -aldoxime yields, with hydriodic acid, benzyl iodide, the β -benzylhydroxylamine forms benzylamine. Consequently the benzyl group in the ether of the β -oxime, and therefore the hydrogen atom in the β -oxime itself, is linked to nitrogen thus:



β -Benzaldoxime benzyl ether.

Benzylamine.

The same explanation served for the isomeric ketoximes. But the argument could not be sustained. In the first place, Auwers and others found that benzaldoxime exhibits tautomerism (p. 182), and the constitution of the aldoxime could not be inferred from that of its

¹ *Ber.*, 1889, 22, 429, 1581.

² *Ber.*, 1889, 22, 1581.

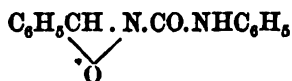
³ *Ber.*, 1890, 23, 1684.

benzyl ethers, added to which the two oxygen-methyl ethers as well as the two nitrogen-methyl ethers of benzaldoxime are actually known (p. 182).¹

In the second place, Goldschmidt² obtained from both benzaldoximes by the action of phenyl carbimide, $C_6H_5N:CO$, under precisely similar conditions, carbanilide compounds, one of which, the β -derivative, is converted into the α -compound by a trace of hydrogen chloride, and both are decomposed by dilute alkalis with equal ease. A compound having the formula of the α -aldoxime would give a carbanilide of the following structure:



whilst, according to Beckmann, the β -oxime would yield a stable urea derivative of the formula:



It is improbable that compounds with such marked structural differences would respond in the same way to the chemical reagents described above.

Finally, it should be mentioned that Hartley and Dobbie³ have satisfied themselves of the structural identity of the two compounds from an examination of the absorption spectra.

STEREOCHEMISTRY OF TERVALENT NITROGEN

Geometrical Isomerism of the Oximes. Van't Hoff in his *Ansichten über die organische Chemie* (1878) was the first to speculate upon the stereochemical possibilities of nitrogen compounds.

If trivalent nitrogen, to take the simplest case, has linked to it three different groups, *a*, *b*, *c*, they may either lie in one plane with the nitrogen atom, when isomerism would be precluded (Fig. 16),

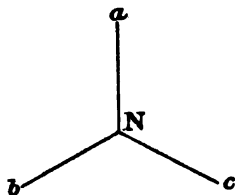


FIG. 16.

¹ Luxmoore, *Trans. Chem. Soc.*, 1896, 69, 177.

² *Ber.*, 1889, 22, 3113.

³ *Trans. Chem. Soc.*, 1900, 77, 509.

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or they may be drawn together by mutual attraction, causing the bonds to be bent along the edges of a tetrahedron. In this case they will no longer lie in the same plane with the nitrogen atom but form an unsymmetrical space arrangement, and stereoisomerism becomes possible.

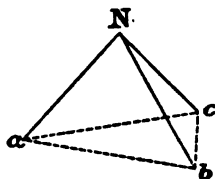


FIG. 17.

Attempts to resolve substituted ammonias¹ like benzyethylamine, *p*-tolylhydrazine, methylaniline, tetrahydroquinoline, &c., by crystallization of their salts with active acids, have invariably failed, and the conclusion seems inevitable that the nitrogen bonds in these compounds lie in one plane with the nitrogen atom.

The experiments are, however, so far inconclusive that partially racemic compounds might be formed, or hydrolytic dissociation of the salts might occur in process of crystallization. In the former case the two enantiomorphous bases would crystallize with the same active acid in equivalent amounts, and, in the second, optical inversion of the nitrogen groups might occur, producing racemisation.

Another suggested cause of failure of the above method is the change of valency of the nitrogen atom in the union of the tervalent bases with acids which might displace the original directions of the bonds. These possible causes of failure have to some extent been avoided by crystallizing the salts from non-hydroxylic solvents, and by using substituted hydrazines of the general formula $\begin{smallmatrix} a \\ b \end{smallmatrix} > \text{N} \cdot \text{NH}_2$, in which the valency of the asymmetrical tervalent group is undisturbed;² but in neither case has any resolution of the bases been effected.

Evidence, but of another kind, of the plane arrangement of the nitrogen bonds has been furnished by Kipping and Salway.³ They have fractionally crystallized the amide resulting from the union of an externally compensated acid chloride, for example, *dl*-benzyl-methyl-acetyl chloride with an unsymmetrical primary amine (e. g. methylaniline). If the amine is externally compensated, two enantiomorphous pairs of compounds should result, namely, *dAdB* and *lAIB*; *dAIB* and *lAdB*, which would form two inactive salts separable by crystallization. As the product was homogeneous, the

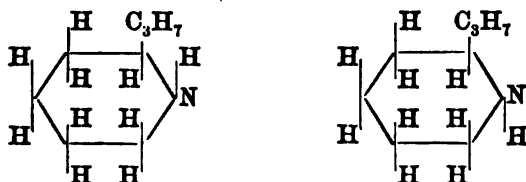
¹ Kraft, *Ber.*, 1890, 23, 2780; Behrend and König, *Annalen*, 1891, 263, 184; Ladenburg, *Ber.*, 1893, 26, 864.

² Reychler, *Bull. Soc. Chim.*, 1902 (3), 27, 979; Jones and Millington, *Proc. Camb. Phil. Soc.*, 1904, 2, 489.

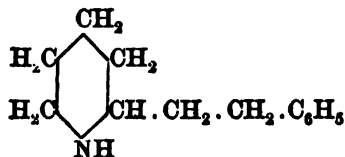
³ *Trans. Chem. Soc.*, 1904, 85, 438.

evidence is in favour of a plane configuration of the tervalent nitrogen compounds.

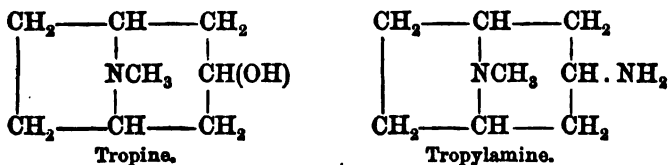
Attempts to resolve such compounds have been more successful where the nitrogen forms part of a ring. Ladenburg¹ found that on distilling conine hydrochloride with zinc dust and a little water, a new substance, *isoconine*, was produced, which differs from conine in its rotatory power and in certain other properties. The difference of the two compounds was ascribed to the hydrogen atom attached to nitrogen, which occupies two positions in relation to the propyl group.



A result which affords a similar explanation has been obtained with artificial *l*-stilbazoline,²



which on heating yields the isomeric *l*-isostilbazoline. The existence of the two tropines and tropanylamine of Willstätter and Müller³ can only be explained by a change in the configuration of the NCH_3 group relatively to the substituted methylene group (p. 582).



Theory of Hantzsch and Werner. The theory of Hantzsch and Werner,⁴ which was put forward to explain the existence of the isomeric oximes, appeared in 1890, and, in spite of some adverse criticism, has successfully held its ground.

¹ Ber., 1893, 26, 854.

² Ber., 1904, 37, 3638.

³ Ber., 1896, 29, 936, 1636, 2228; 1898, 31, 1212, 2655.

⁴ Ber., 1890, 23, 11.

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Based on recognized stereochemical principles, it afforded at the time of its publication a simple explanation of existing facts, and has since become a fruitful source of new discoveries.

Hantzsch and Werner point out that in compounds like hydrocyanic acid, cyanogen, pyridine, thiazole and other cyclic nitrogen compounds in which nitrogen is linked to carbon, if the carbon bonds are directed towards the summits of a tetrahedron, a corresponding bending of the nitrogen linkages is probable (Fig. 18).

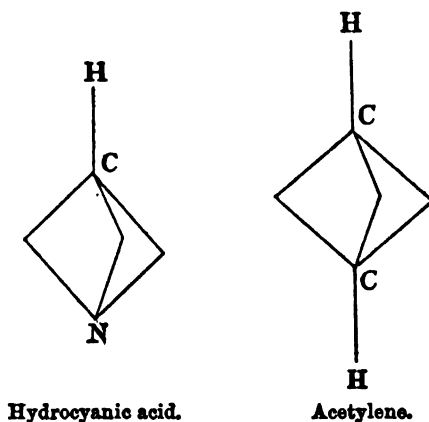


FIG. 18.

A configuration of this character will correspond to acetylene and cannot furnish isomeric derivatives (p. 108); but supposing that whilst the direction of the carbon and nitrogen bonds in hydrogen cyanide is preserved one pair is severed, the nitrogen and carbon become doubly linked as in ethylene and its derivatives. Represented by tetrahedral models (nitrogen occupies the summit of one tetrahedron), the two space arrangements will be represented thus :

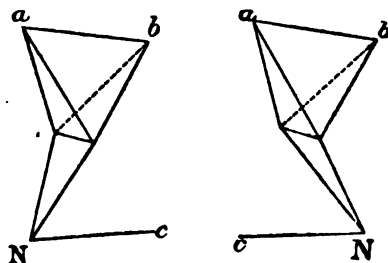


FIG. 19.

If the Kekulé models are substituted, the formulae will appear as follows :

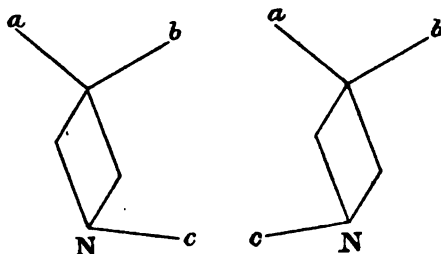
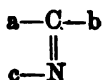
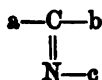


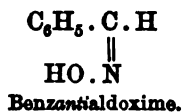
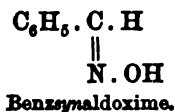
FIG. 20.

Just as geometrical isomerism may occur in ethylene derivatives when the doubly linked carbon atoms are united to a different pair of groups, so in the present case two substances are conceivable, in which doubly linked nitrogen and carbon are present. The configurations may be conveniently represented in the following way :

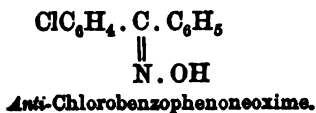
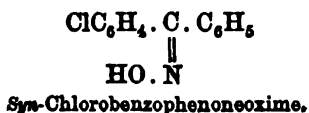


Precisely these conditions obtain in the unsymmetrical oximes.

The two benzaldoximes may be represented by the following configurations, which are distinguished by the prefix *syn* and *anti*, which correspond to *cis* and *trans* respectively in the ethylene series.

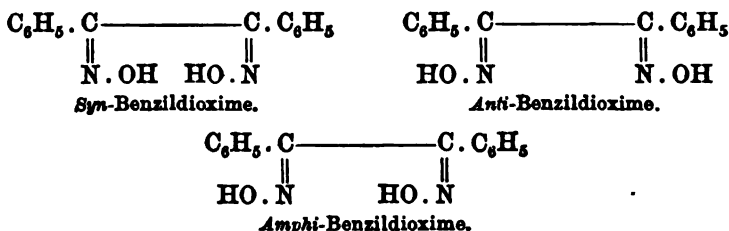


In the case of the aldoximes and monoketoximes the term *syn* precedes the name of the group occupying the *cis* position to the hydroxyl of the oximino group, whilst *anti* indicates the reverse arrangement. The two *p*-chlorobenzophenoneoximes will appear thus :



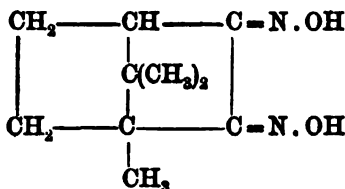
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The three benzildioximes are distinguished by the terms *syn*, *anti*, and *amphi*.



The number of actual isomers in each of the above examples corresponds exactly to that required by the theory.

Camphor dioxime should exist in four different configurations :

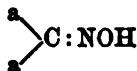


All four are known.

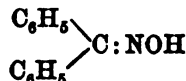
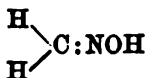
Properties of the Isomers. The isomers are not characterized by optical differences, but by those physical and chemical properties which distinguish the geometrical isomers of the ethylene series (p. 108). In addition they are readily convertible into one another, and, most significant of all, isomerism disappears where theory demands it. Thus, the benzaldoximes give the same benzyl hydroxylamine on reduction,



and isomeric ketoximes of the formula,



like formaldoxime and diphenylketoxime, have never been prepared,



whilst acetaldoximes and propionaldoximes as well as a variety of aldoximes and unsymmetrical ketoximes of the aromatic series are known. In short, the experimental facts satisfy all the essential conditions of geometrical isomerism.

The impulse which the theory of Hantzsch and Werner has given to the search for new examples of stereoisomerism among this class of compounds has rapidly added to the number, and the list has grown to formidable proportions. The following are among the better known examples:¹

Aldoximes.

<i>o</i> - <i>m</i> - and <i>p</i> -Nitrobenzaldoxime	Anisaldoxime
<i>o</i> - <i>m</i> - and <i>p</i> -Chlorobenzaldoxime	Cuminaldoxime
<i>m</i> - and <i>p</i> -Bromobenzaldoxime	Piperonaldoxime
<i>p</i> -Iodobenzaldoxime	Furfuraldoxime
<i>m</i> - and <i>p</i> -Tolylaldoxime	Thiophenaldoxime

Ketoximes.

<i>p</i> -Methoxybenzophenoneoxime	<i>p</i> -Propylbenzophenoneoxime
<i>m</i> - <i>p</i> -Chlorobenzophenoneoxime	Xylylbenzophenoneoxime
<i>m</i> - <i>p</i> -Bromobenzophenoneoxime	<i>p</i> -Aminobenzophenoneoxime
<i>o</i> - <i>p</i> -Tolylphenylketoxime	<i>m</i> - <i>p</i> -Hydroxybenzophenoneoxime
<i>p</i> -Ethylbenzophenoneoxime	Thienylphenylketoxime

Dioximes.

Benzildioxime	Nitrobenzildioxime
Anisildioxime	Phenylglyoxime
Cuminildioxime	Glyoximedicarboxylic acid
Tolildioxime	Camphordioxime

Quinoneoximes.

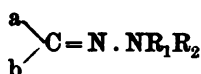
Methyl <i>m</i> -chloroquinoneoxime	$\text{O} = \text{C}_6\text{H}_3(\text{Cl}) = \text{N} \cdot \text{O} \cdot \text{CH}_3$
Benzoyl <i>m</i> -chloroquinoneoxime	$\text{O} = \text{C}_6\text{H}_3(\text{Cl}) = \text{N} \cdot \text{O} \cdot \text{COC}_6\text{H}_5$
<i>p</i> -Chlorotoluquinoneoxime	$\text{O} = \text{C}_6\text{H}_3(\text{Cl})(\text{CH}_3) = \text{NOH}$
<i>p</i> -Bromotoluquinoneoxime	$\text{O} = \text{C}_6\text{H}_3(\text{Br})(\text{CH}_3) = \text{NOH}$

In addition to the oximes of aldehydes, ketones, diketones, and quinones, isomers belonging to the class of hydrazones, osazones,

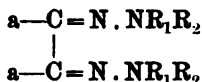
¹ A more complete list will be found in Werner's *Lehrbuch der Stereochemie*.

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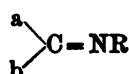
anil-compounds, chlorimides, and diazo-compounds, all of which contain the requisite doubly-linked carbon-nitrogen or nitrogen-nitrogen complex, are now known:



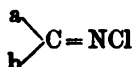
Hydrazones.



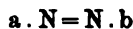
Osazones.



Anil compounds.



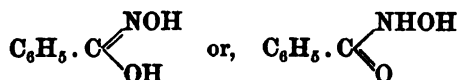
Chlorimides.



Diazo-compounds.

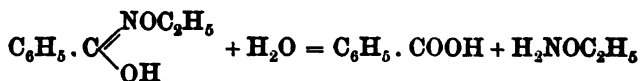
Lossen's Benzhydroxamic Acid and its Derivatives. The theory has moreover accounted for some of the mysterious *physical isomers* which Lossen¹ found among the derivatives of benzhydroxamic acid.

Benzhydroxamic acid, or benzhydroximic acid, as Werner² prefers to call it, is obtained by the action of benzoyl chloride or benzoic ester on hydroxylamine



Benzhydroximic acid.

The ethyl ether, prepared by the action of ethyl iodide on the potassium salt, has the following formula, since it is decomposed by dilute acids into benzoic acid and ethoxylamine:

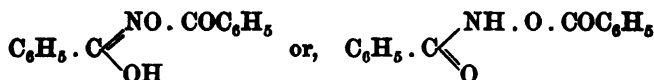


Benzhydroximic ether.

Benzoic acid.

Ethoxylamine.

The hydrogen of the hydroxylamine-hydroxyl may also be replaced by acid radicals, such as benzoyl, as well as by alkyl groups. The compounds with acid radicals are acids and form salts. The formula of the benzoyl derivative will be one of the following:

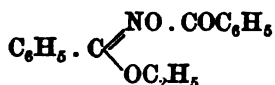


If now the replaceable hydrogen is substituted by an alkyl group, by the action of alkyl iodide on the silver salt, the product (as well

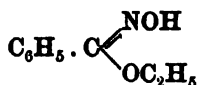
¹ *Annalen*, 1872, 161, 347; 1875, 175, 271; 1877, 186, 1; 1889, 252, 170; 1891, 265, 176; 1894, 281, 169.

² *Ber.*, 1892, 25, 27; 1893, 26, 1561; 1896, 29, 1155.

as that obtained by its hydrolysis, namely, ethyl benzhydroximic acid) is found to be a mixture of two isomers :



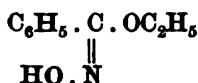
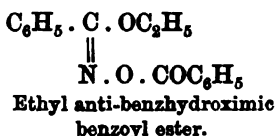
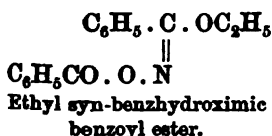
Ethyl benzhydroximic benzoyl ester.



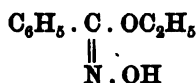
Ethyl benzhydroximic acid.

Both of the ethyl benzhydroximic acids decompose on hydrolysis into benzoic ester and hydroxylamine.

Werner has pointed out that these compounds are strictly oximes, and offer a striking analogy in chemical behaviour to the isomeric ketoximes. The reason for this becomes apparent on making a slight alteration in the manner of writing the formula :



Ethyl syn-benzhydroximic acid.



Ethyl anti-benzhydroximic acid.

The following are the names of some of the hydroximic acids which exist in isomeric forms :

Hydroximic acids.

Propylbenzhydroximic acid	$\text{C}_6\text{H}_5 \cdot \text{C}(\text{NOH})\text{OC}_3\text{H}_7$
Ethyl <i>p</i> -tolylhydroximic acid	$\text{CH}_3\text{C}_6\text{H}_4\text{C}(\text{NOH})\text{OC}_2\text{H}_5$
Ethylanishydroximic acid	$\text{CH}_3\text{OC}_6\text{H}_4\text{C}(\text{NOH})\text{OC}_2\text{H}_5$

Hydroximic esters.

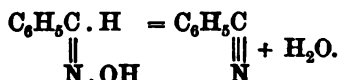
Propylbenzhydroximic benzoyl ester	$\text{C}_6\text{H}_5\text{C}(\text{NOCOC}_6\text{H}_5)\text{OC}_3\text{H}_7$
Ethyl <i>p</i> -tolylhydroximic benzoyl ester	$\text{CH}_3\text{C}_6\text{H}_4\text{C}(\text{NOCOC}_6\text{H}_5)\text{OC}_2\text{H}_5$
Ethylanishydroximic benzoyl ester	$\text{CH}_3\text{OC}_6\text{H}_4\text{C}(\text{NOCOC}_6\text{H}_5)\text{OC}_2\text{H}_5$
Ethylanishydroximic anisyl ester	$\text{CH}_3\text{OC}_6\text{H}_4\text{C}(\text{NOCOC}_6\text{H}_4\text{OCH}_3)\text{OC}_2\text{H}_5$
Ethylbenzhydroximic anisyl ester	$\text{C}_6\text{H}_5\text{C}(\text{NOCOC}_6\text{H}_4\text{OCH}_3)\text{OC}_2\text{H}_5$

Determination of Configuration. We have now to consider the methods adopted by Hantzsch for determining the configuration of

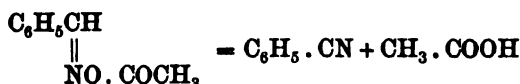
the isomeric oximes. The methods, like those applied to ethylene derivatives, are based on some marked difference in chemical behaviour, and especially on intramolecular changes such as the formation of anhydrides.

Configuration of the Aldoximes. It is found that one of the isomeric aldoximes decomposes into a nitrile more readily than the other. This property is taken to indicate the *syn* configuration.

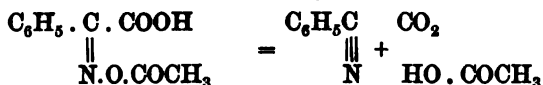
Thus benzsynaldoxime forms benzonitrile and water,



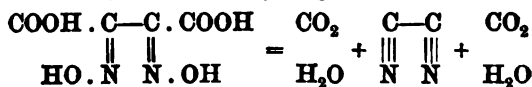
The reaction is generally performed by warming the aldoxime with acetic anhydride (when the acetyl derivative is formed), cooling, adding solid sodium carbonate, and finally a solution of caustic soda. Under these conditions the anti-compound is unattacked, and dissolves in the alkaline solution, whilst the nitrile from the *syn*-compound remains undissolved and is readily detected by its strong and characteristic smell:



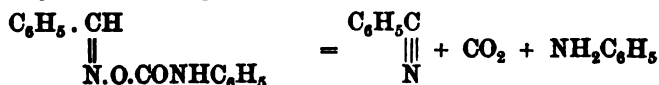
The two phenyloximino-acetic acids¹ may be distinguished by the same process. The acetyl derivative of the one yields benzonitrile, that of the other is hydrolysed and gives the original oximino compound. The first has therefore the *syn* configuration:



Antiglyoxime dicarboxylic acid behaves in the same manner and gives carbon dioxide, water, and cyanogen:

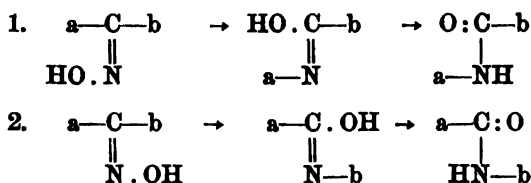


The behaviour of carbanilide compounds of the aldoximes can also be employed for determining configuration. One of the isomers (probably the *syn*-compound) undergoes decomposition either spontaneously or on heating, and yields the nitrile:



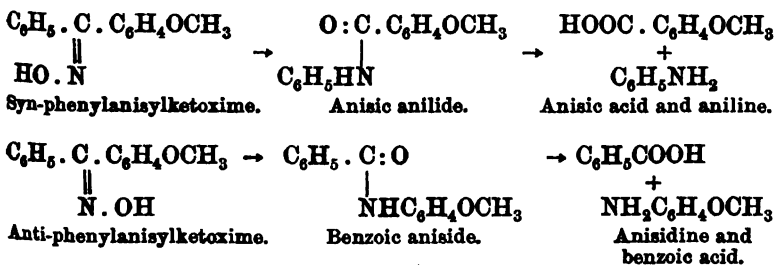
¹ Hantzsch, *Ber.*, 1891, 24, 41.

Configuration of the Ketoximes. In determining the configuration of the ketoximes Hantzsch employs what is known as Beckmann's reaction. When the ketoximes are treated with strong sulphuric acid, hydrochloric acid, or phosphorus chloride, a molecular change occurs whereby the oxime is converted into an amide. To prevent conversion of one isomer into the other during the process, it is found advisable to use phosphorus pentachloride in preference to the other reagents, and to add it to the compound in a cold solution of benzene or petroleum spirit. The reaction has been explained in the following manner. The hydroxyl group attached to the nitrogen atom changes place with the radical attached to the carbon atom in the *cis* position. This is followed by the shifting of the hydroxyl-hydrogen from the oxygen to the nitrogen (see p. 180). The character of the product will consequently depend on the relative positions of the hydroxyl group and radical in the oxime. If *a* and *b* denote the two radicals the changes will proceed as follows:



The amine and acid obtained by decomposing the amide will be different in the two cases.

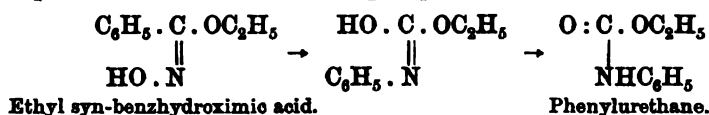
Thus, there are two isomeric *p*-methoxybenzophenoneoximes *m. p.* 187° and 115°. The one phenylanisylketoxime yields anisic anilide and finally anisic acid and aniline, and is therefore the *syn*-compound, whereas the other is converted into benzoic aniside and then anisidine and benzoic acid, and is consequently the *anti*-compound:



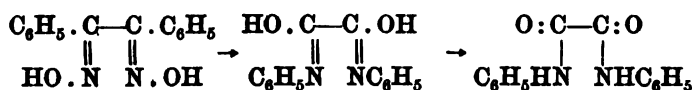
Configuration of the Hydroxamic Acids. The same reaction may be used for identifying the ethylbenzhydroxamic acids, for the *α*-acid

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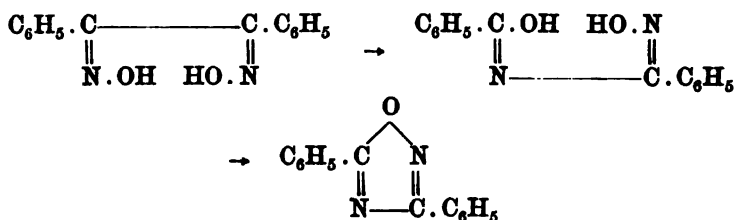
(syn) changes into phenylurethane, whereas the β -acid (anti) is undecomposed and combines with the phosphorus to form an ester :



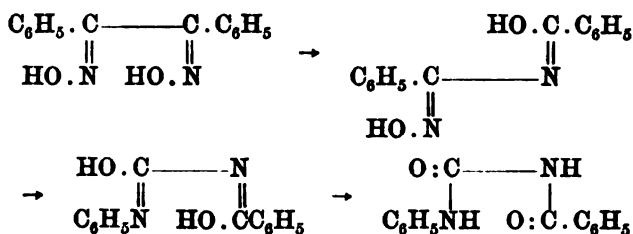
Configuration of the Dioximes or Glyoximes. The behaviour of glyoximedicarboxylic acid has already been mentioned (p. 148). The benzildioximes and analogous compounds can be differentiated by the aid of Beckmann's reaction. The most stable (β) of the benzildioximes, since it yields oxanilide, is the anti-compound :



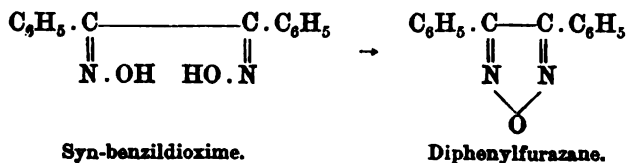
The α -compound gives dibenzylazoxime and is therefore the syn-compound:



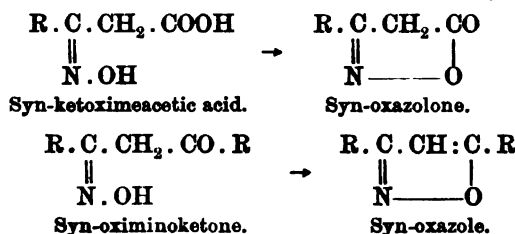
whilst the γ -dioxime is converted into benzoylphenylurea and represents the amphi-compound :



The syn-dioximes are further characterized by the formation of anhydrides or furazanes :



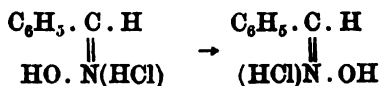
The same property can be utilized to determine configuration in such cases as the β -ketoximic acids of the formula $R.C(NO_2).CH_2.COOH$ and β -oximinoketones $R.C(NO_2).CH_2.CO.R$, even though no second isomer is known. Both groups of compounds form anhydrides more or less readily, and possess, therefore, a syn configuration :



Inversion of the Oximes. The manner in which the oximes undergo conversion into one another has already been illustrated in the case of the benzaldoximes and benziloximes (pp. 186, 188). Heat, light, and crystallization will sometimes effect the change, but hydrogen chloride in presence of benzene, ether, or alcohol is the most common and effective reagent for transforming the anti-aldoxime into the hydrochloride of the syn-compound provided that water is excluded. If water is present the reverse change may occur, and frequently the syn-compound in the free state passes spontaneously into the anti-compound.

The alkyl derivatives of the aldoximes change, if they change at all, in the direction from the syn- to the anti-compound. There is no question of a reversible change in the sense that a definite equilibrium mixture of the two products is formed. It is usually complete in one direction.¹ The behaviour of the two isomers must be explained by the relative stability of the free oximes and their salts.

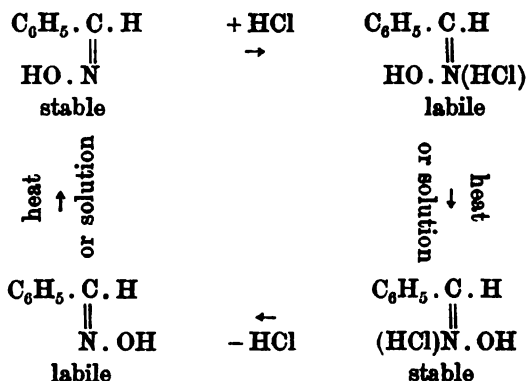
It is clear that in the case of the benzaldoximes the syn-compound is labile in the free state, whereas it forms a stable hydrochloride. Luxmoore² has shown, for example, that hydrochloric acid gas passed into an ethereal solution of benzantialdoxime at 0° precipitates the anti-hydrochloride; but on attempting to recrystallize it, it was converted by simple dissolution into the hydrochloride of the syn-compound, and a similar change was observed to take place slowly at the ordinary temperature :



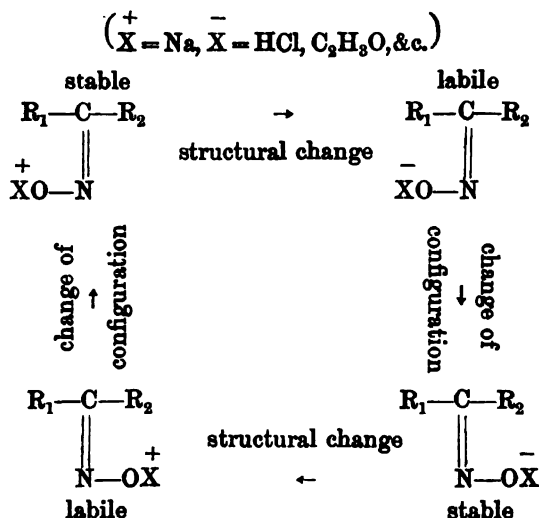
¹ Hantzsch, *Zeit. phys. Chem.*, 1894, 13, 509.

² *Trans. Chem. Soc.*, 1896, 69, 181.

As soon as the syn-aldoxime is liberated by the addition of alkali, or its hydrochloride becomes dissociated by the addition of water, it reverts to the anti-compound. This cycle of changes may be represented by the following scheme:



Hantzsch¹ divides the oximes into the *acid stable* and the *alkali stable* and formulates the more general scheme:



All the dioximes such as the dioximes of benzil, phenylglyoxal, glyoxal dicarboxylic acid, as well as the oximes of *p*-hydroxybenzophenone and phenylglyoxylic acid, exhibit this behaviour, which explains, among other things, the formation of the one isomer by

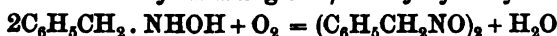
¹ *Grundriss der Stereochemie*, 2nd ed. p. 180.

the action of free hydroxylamine in the presence of alkali, and the other by the use of the hydrochloride (p. 187).

The instability of the anti-compounds in presence of acids, especially hydrochloric acid, accounts for the action of acetyl chloride, which, by producing traces of hydrogen chloride, converts benzanti-aldoxime into the acetyl derivative of the syn-compound; hence the substitution of acetic anhydride in the method described for determining configurations. It explains also the use of carbon dioxide for liberating the anti-benzaldoxime from its sodium salt (p. 188).

Comstock¹ has made the curious observation that the aldoximes form compounds with cuprous chloride and bromide of the formula $(R \cdot CH:NOH)_2CuX$, and here again the salt is that of the syn-aldoxime.

It is readily conceivable from what has been stated that the formation of the particular isomer is dependent on the chemical or physical conditions of the experiment, and that it is rather the exception than the rule to find both isomers in the product. Nevertheless, isomeric ketoximes of the aromatic series frequently appear together when the oxime is formed in alkaline solution by Auwers' method,² and they can then be separated by fractional crystallization. The simultaneous formation of the two aldoximes has been observed in the process of decomposing the bisnitrosylbenzyl compounds.³ The latter are formed by oxidizing the β -benzylhydroxylamines,



and with sodium ethylate yield a mixture of the two geometrical isomers:



But in other cases the two compounds are derived from different materials, one oximino-succinic ester, for example, being prepared by the action of nitrous acid on succino-succinic ester, and the other by the action of hydroxylamine on oxaloacetic ester⁴:



Oximino-succinic ester.

Stability of the Isomeric Oximes. It must not be supposed that in all cases the number of isomers corresponds to that demanded by the theory. The unsymmetrical monoximes do not always exist in two forms. In many cases the isomer is missing. Among the aromatic aldoximes only one oxime of *o*-tolylaldoxime, *o*-anisaldoxime,

¹ *Amer. Chem. J.*, 1897, 19, 485.

² *Ber.*, 1889, 22, 604.

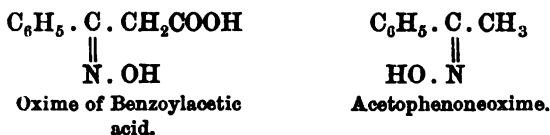
³ *Werner's Lehrbuch der Stereochemie*, p. 270.

⁴ *Ebert, Annalen*, 1885, 229, 65; *Piutti, Ber.*, 1891, 24, 2287.

and salicylaldoxime is known, whilst, with the exception of acetaldoxime, oenanthaldoxime, and possibly propionaldoxime, no stereoisomeric representatives of the aliphatic aldoximes exist. The single aromatic aldoximes mentioned above are anti-aldoximes; the majority of aliphatic aldoximes, on the other hand, are syn-compounds. This result is significant when combined with the fact, already discussed, that oximes in the free state frequently exhibit marked differences in stability. Hantzsch attributes the difference to the nature of the radicals attached to the doubly-linked carbon atom, which may attract or repel the oxime-hydroxyl in its vicinity. Working on this basis and from a careful study of a variety of aldoximes and ketoximes, Hantzsch has drawn up a table of radicals which are arranged in the order of decreasing attraction for the hydroxyl group. The principal members are:

1. $\text{COOH} \cdot \text{CH}_2$; 2. COOH ; 3. C_6H_5 ; 4. $\text{C}_6\text{H}_4\text{X}$; 5. $\text{C}_4\text{H}_3\text{S}$;
6. $\text{C}_n\text{H}_{2n+1}$; 7. CH_3 .

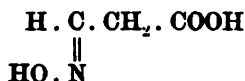
It follows from this table that the syn configuration will exhibit greater stability in the case of compounds containing radicals which attract the hydroxyl-group, whilst in those in which the radical repels the hydroxyl, the anti configuration will be the more stable. If the instability of the second isomer is such as to prevent its existence under ordinary conditions, the absence of the anti configuration of the oxime of benzoylacetic acid and of the syn configuration of acetophenone is readily accounted for:



The absence of one isomer is more likely to occur where the radicals are drawn from the extremes in the scale, whilst oximes containing radicals drawn from the middle would appear to have a better chance of a stereoisomeric existence. Experience seems to justify this conclusion. Ketoximes $\text{C}_6\text{H}_5 \cdot \text{C}(\text{NOH}) \cdot \text{C}_6\text{H}_4\text{X}$, containing the aromatic radicals 3 and 4, form sufficiently stable syn and anti configurations to be isolated without difficulty and present the greatest variety of examples of this kind of isomerism. The relative stability of these compounds is also subject to variation depending on the nature as well as on the position of the radical X.

A word must be added on the position of hydrogen in the scale. Its behaviour seems capricious. Whilst in aldoximeacetic acid,

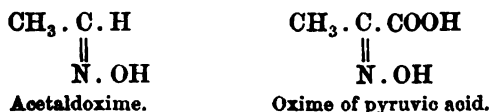
hydrogen, by its strong attraction for hydroxyl, appears at the opposite end of the scale to methyl



it shows the very reverse behaviour in the benzaldoximes, in which, especially in the ortho series (p. 154), it has strong proclivities for the aromatic radical.

The order of attraction of the radicals for the hydroxyl will naturally make its influence felt in the process of chemical change, and it is scarcely surprising that such decomposition as the formation of nitriles from the aldoximes and ketoximecarboxylic acids, as well as the production of anhydrides, should vary with the nature of the radicals.

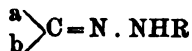
Syn-aldoximes and carboxylic acids of the aliphatic series, such as acetaldoxime and the oxime of pyruvic acid,



form acetyl derivatives which spontaneously yield the nitriles, whilst if the alkyl is replaced by an aryl radical the decomposition is retarded.

Sufficient has been said to indicate how much less decisive are the methods available for studying the configuration of the oximes than is the case in the ethylene series.

Hydrazones. Stereoisomeric hydrazones of the general formula



frequently appear together in the course of preparation by the ordinary process from ketones and hydrazines, and can then be separated by fractional crystallization. In other cases the one is transformed into the other by the action of reagents. Fehrlin¹ observed that the hydrazone of *o*-nitrophenylglyoxylic acid yields an isomer on dissolving it in alkalis, and the two compounds have different melting-points, crystalline appearance, and solubilities, but form the same product on reduction. Different materials may occasionally give rise to the two isomers. One of the isomeric phenylhydrazones of anisylphenylketone is obtained from the ketone

¹ Ber., 1890, 23, 1574.

chloride, whilst the second is derived from the ketone itself.¹ They differ in appearance and solubility, and one is slowly transformed in alcoholic solution into the other. The subsequent discovery of two diphenylhydrazones of anisylphenyl ketone, which were obtained in the same way, excluded the probability of structural differences in the two series of isomers.

Anschütz and Pauly obtained from dihydroxy-tartaric ester three isomeric diphenylhydrazones, two of which pass into the third by heating the solution, or by the action of traces of iodine or sulphur dioxide. Two hydrazones of benzoyl-formaldehyde were prepared by Bamberger and Schmidt, and isomeric hydrazones of aldehydes have also been obtained from benzaldehyde, nitroformaldehyde, salicylaldehyde, and protocatechuic aldehyde.

In addition to these the following important hydrazones exist in stereoisomeric forms:

Hydrazones.

Acetaldehydephenylhydrazone

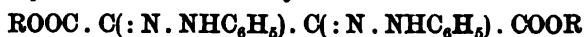
Benzoinphenylhydrazone

Cyanacetic ester phenylhydrazone

Cyanacetic ester *o*- and *p*-tolylhydrazone,

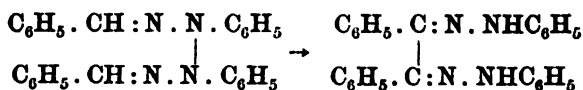
and other substituted phenylhydrazones of cyanacetic ester.

Osazones. Stereoisomeric osazones are also known. Geldermann obtained an osazone of glyoxal dicarboxylic ester, *m. p.* 120–121°, by the action of phenylhydrazine in alcoholic solution. Two other isomers, making up the theoretical number, were subsequently prepared by Anschütz and Pauly.²



Osazone of glyoxal dicarboxylic ester.

One osazone of benzil, *m. p.* 208°, is prepared by the usual process, that is, by the action of phenylhydrazine on benzil. The second was obtained by Ingle and Mann³ in the following interesting way. By the action of sodium ethoxide and then of iodine on the alcoholic solution of benzalphenylhydrazone, dibenzalphenylhydrazone is formed, which on boiling with alkali undergoes isomeric change and passes into the second benzilosazone *m. p.* 225°:



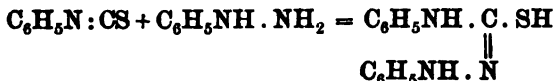
¹ Hantzsch and Kraft, *Ber.*, 1891, 24, 3511; Hantzsch and Overton, *Ber.*, 1893, 26, 9.

² *Ber.*, 1895, 28, 64.

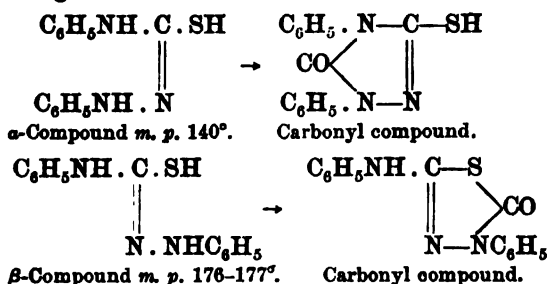
³ *Trans. Chem. Soc.*, 1895, 69, 606.

Isomeric osazones of salicil, anisil, and piperil, have also been obtained. The configurations of these substances are still doubtful as no trustworthy method for ascertaining them has yet presented itself.

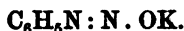
Diphenylthiosemicarbasides. A number of thiosemicarbazide compounds are described by Marckwald. Phenylhydrazine combines with phenylthiocarbimide on heating the alcoholic solution of the mixture thus:



The product or α -compound melts at 140° , then solidifies, and melts again at 176 – 177° , forming the β -compound. Heating with a drop of hydrochloric acid also brings about the conversion. Each compound gives a different product with carbonyl chloride, from which the configuration can be ascertained:



Stereochemistry of the Diazo-compounds. Many years ago Griess found that when a concentrated solution of caustic potash is added to diazobenzene chloride, a colourless crystalline potassium diazotate is deposited, which, in conformity with Kekulé's formula for diazobenzene, appeared as follows:



In 1894 Schraube and Schmidt¹ made the curious observation that if diazobenzene chloride and strong potash solution are heated to 130 – 140° a new crystalline compound of great stability is formed, which is isomeric with Griess's salt. Two isomeric derivatives of *p*-nitrodiazobenzene were obtained in a similar way. Not the least remarkable of the characteristics of the new and stable isodiazotates is their inability to give azo-colours when added to an alkaline solution of a phenol, a property which is entirely contrary to the ordinary behaviour of diazobenzene salts. This property is, however, regained

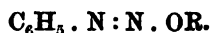
¹ Ber., 1894, 27, 514.

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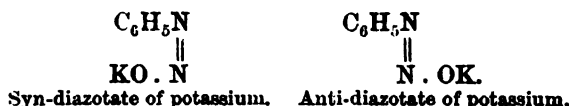
if the potassium salt is first acidified and then brought into the alkaline solution of the phenol. Further investigation showed that if the isodiazotate of potassium is acted on with an alkyl iodide or acyl chloride, a phenylnitrosamine derivative is formed of the formula $C_6H_5NR.NO$, and for this reason Bamberger regarded the new compound as the potassium salt of phenylnitrosamine:



The insufficiency of this deduction was shortly afterwards pointed out by von Pechmann, who, by using the silver salt in place of the potassium compound, prepared the isomeric ethers, having the formula:

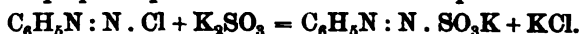


The case is precisely parallel to that of the amides and aldoximes and many other compounds which exhibit tautomerism (p. 183). Hantzsch, without, it must be admitted, any very clear evidence, explained the isomerism of the two diazotates by a space arrangement of the ethylene or oxime type. The unstable potassium compound represented the syn, the stable salt, the anti configuration:



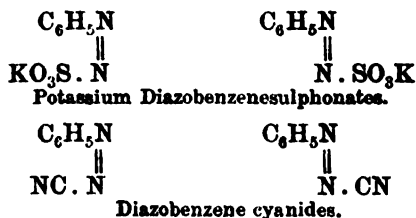
But the view very soon received substantial support from Hantzsch's discovery of a second diazobenzene sulphonate and diazobenzene cyanide; for, unlike the diazotates, these substances possess no mobile hydrogen atom, and do not admit of tautomeric change.

By the action of potassium sulphite on diazobenzene chloride Fischer had prepared potassium diazobenzene sulphonate:

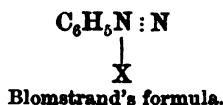


By performing the same reaction at a low temperature and in presence of sodium carbonate, the new and highly unstable sulphonate is obtained. The production of the two cyanides is effected in a similar manner.

Hantzsch expressed the constitution of these compounds as follows:

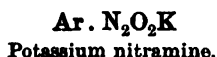


This view was strenuously opposed by Bamberger, who adhered to the opinion that structural and not stereoisomeric differences underlie the constitution of the two series of compounds. After a long controversy a partial *rapprochement* between the views of Hantzsch and Bamberger was at length reached. Both observers are now disposed to accept, at least as regards the salts of diazobenzene with the stronger acid radicals, which do not exhibit isomerism, the formula proposed in 1875 by Blomstrand. These compounds behave like ammonium salts, inasmuch as they form neutral salts and appear from their electrical conductivities to be dissociated in aqueous solution. They probably contain, like the ammonium salts, quinquivalent nitrogen, and have the following general formula (X = acid radical):



From their analogy with the salts of ammonium they received the name of *diazonium* salts, and the group $\text{C}_6\text{H}_5\text{N}:\text{N}$ was called the *diazonium* group. But whilst Bamberger explains the two series of isomeric diazo-compounds by the diazonium and diazo formulae, that is, as differing in structure, Hantzsch retains for the alkaline diazotates, the diazosulphonates, and cyanides their former stereoisomeric relations.

Structural Identity of the Diazo-compounds. The reasons advanced by Hantzsch for regarding each pair of the series of isomeric diazo-compounds as structurally identical are briefly as follows; the alkaline diazotates are colourless salts resembling those of the oximes of the general formula $>\text{C}:\text{N}$. OK. Though more or less hydrolysed in aqueous solution, like salts of the oximes, it is unlikely that either salt is the alkaline derivative of diazonium hydrate, which is a strong base like potassium hydroxide. Moreover, both diazotates behave chemically alike; they are reduced to hydrazones, give with benzoyl chloride, nitrosoacylanilides, and yield nitramine salts on oxidation (Ar = *aryl*):

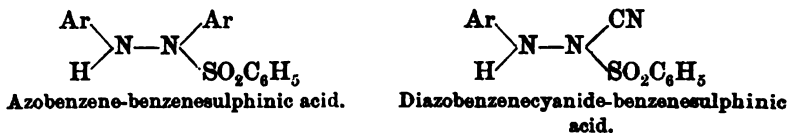


The diazosulphonates dissociate into two ions, K^+ and $\text{ArN}_2\text{SO}_3^-$, which are yellow or reddish yellow in colour. They are, therefore, not diazonium salts, for they should then break up into the colourless ions ArN_2^+ , SO_3^- , and K^+ . As alkalis do not form sulphonates, but sulphites, which are decomposed by acids, it is unlikely that

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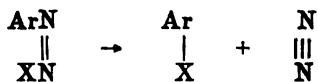
either substance in question is a diazonium sulphite, seeing that in addition to being coloured they fail to give the ordinary sulphite reactions.

The isomeric diazocyanides differ from alkaline cyanides in being sparingly soluble in water and in showing little tendency to evolve hydrocyanic acid on the addition of acids, but, like azo-compounds, they are coloured and dissolve in the common organic solvents. They both yield diazoamino-compounds and diazoimino-ethers with the elimination of cyanogen, and like azobenzene form additive compounds with benzenesulphinic acid :

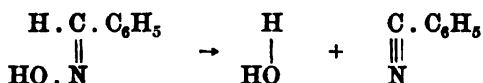


Configuration of the Diazo-compounds. The distinction between the syn and anti configuration of the diazo-compounds does not appear to be so sharply defined as between the syn- and anti-oximes, nor are the examples of isomerism as numerous.

Hantzsch assumes similar relations to exist between these two series of diazo-compounds as between the stereoisomeric ethylenes and oximes, that is to say, the syn-compounds, being the less stable, are the more reactive; they contain more available energy. It follows that the isomer, which is the more easily reduced and oxidised, the more readily converted into the nitrosamide, and the more quickly combined with phenol to form an azo-colour, is the syn-compound. It is probably the syn-compound also which undergoes the ordinary decompositions in which nitrogen is eliminated, although Hantzsch considers that the diazonium salts are directly susceptible of the same change :



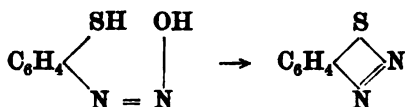
The reaction is parallel to the breaking up of the syn-aldoxime :



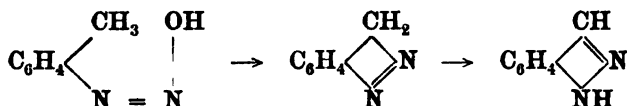
It is also the syn-compounds which, like the cis ethylenes and syn-oximes, have the lower melting-point and the greater solubility. The syn-diazotates, sulphonates, and cyanides all behave similarly.

The anhydride formation so characteristic of cis- and syn-compounds

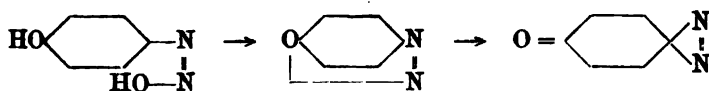
has its probable counterpart in the production of Jacobsen's diazo-sulphide,



of Bamberger's indazole,



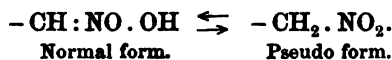
and of Wolff's¹ and Hantzsch's² quinone diazides,



Analogous anti-reactions are unknown.

Isomeric Change of Diazo-compounds. The syn-compounds follow Ostwald's rule, according to which the more labile compound of two isomers is first formed, but as most syn-compounds pass spontaneously into the anti configuration, and as the change is not reversible in the ordinary sense, their isolation requires special conditions. It is usually effected by the action of caustic potash, potassium sulphite, or potassium cyanide on the diazonium salts in alkaline solutions and at low temperatures. It should be added that the greater lability of the syn-compound is not an invariable rule, for tribromodiazobenzene cyanide, $\text{Br}_3\text{C}_6\text{H}_2\text{N}_2\text{CN}$, can only with difficulty be converted into the anti form. The result must be ascribed to the presence of bromine in the nucleus, a fact which introduces the interesting question, to be presently considered, of the effect of nuclear substitution on the stability of the isomers.

There appears to be a close connection between the diazonium salts and the syn-diazo-compounds, a relation which Hantzsch characterizes by describing the syn-compounds as pseudo-diazonium compounds. The term is intended to imply a kind of 'isomeric change', or 'ionic isomerism', such as nitro-compounds and many other substances exhibit in aqueous solution when they pass from the normal to the pseudo condition (see p. 182):

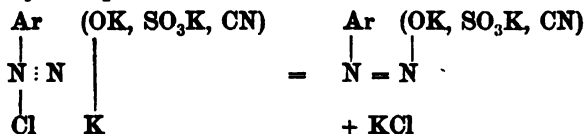


¹ *Annalen*, 1900, 312, 126.

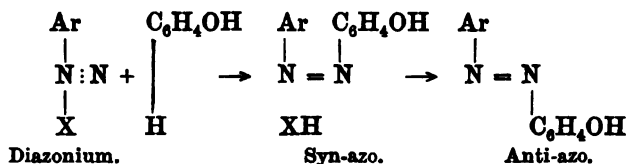
² *Ber.*, 1902, 35, 888.

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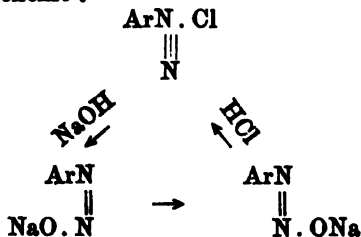
This isomeric change of diazonium to syn-diazo or pseudo-diazonium salts may be represented as follows :



The diazonium or normal salts are stable in presence of acids, but pass into the syn-diazo configuration in presence of alkalis, alkaline sulphites, or cyanides. The reverse change is effected by acids. Translated into electrolytic parlance, the first change is accelerated by hydroxyl ions, the second by hydrogen ions. In dilute aqueous solution both compounds may be present and give rise to equilibrium mixtures. As the diazonium salts are colourless, whilst the diazo-sulphonates and cyanides are coloured, the change may be observed from the colour of the solution. Anisidiazocyanide in dilute aqueous solution partially dissociates into the colourless diazonium cyanide; in stronger solutions the coloured diazocyanide is present. In the process of azo-colour production or coupling, Hantzsch considers that the syn-compound is first formed, and passes into the anti configuration :



In the light of this explanation many obscure changes become clear. It has been stated that the anti-diazotates lose the power of coupling with phenols until the solution has first been made acid and then alkaline. The acid converts the anti-compound into the diazonium salt, which in alkaline solution passes into the labile syn-diazo configuration. Indirectly, therefore, the anti may pass into the syn configuration, thus completing a cycle of changes represented by the following scheme :



In conclusion, a word may be added on the effect of different

elements or radicals in determining the stability of the above three forms of diazo-compounds.

Hantzsch points out that the more positive the character of X in $\text{Ar.N}_2\text{X}$ the greater is the tendency towards the formation of the diazo complex. Thus, whilst the chlorides are colourless, the diazo-bromides, thiocyanates, and iodides in the solid state are coloured, the colour increasing in intensity in the order of the salts given. Positive groups in the nucleus, on the other hand, favour the diazonium type, negative groups the diazo type. Thus, trimethyl syn diazo-benzene cyanide exhibits a tendency to dissociate into a diazonium ion, whilst the tribromo-derivative has the opposite effect, and forms a stable diazo-compound. In the same way the conversion of syn into anti diazo-compounds is retarded by positive and accelerated by negative groups.

Azo-compounds which should exhibit isomerism of the diazo type are not known with certainty. It is still doubtful whether the two trinitro-azotoluenes and *p*-azoxytoluenes of Janovsky¹ owe their existence to stereoisomeric differences.

STEREOCHEMISTRY OF QUINQUEVALENT NITROGEN.

The discovery of stereoisomers among unsymmetrical derivatives of carbon has naturally directed attention to the derivatives of quinquivalent nitrogen and furnished chemists with an attractive theme for experimental inquiry. In constructing a space formula for quinquivalent nitrogen compounds, two conditions must be kept in view. By analogy with the tetrahedral form applied to carbon, the geometrical figure should be of a simple, symmetrical type. Further, it must be remembered that the quinquivalent nitrogen compounds are usually derived from tervalent compounds by addition of two groups (of which one is acidic), and, from what has been previously stated, the three groups in tervalent compounds are in one plane with the nitrogen atom.

Van 't Hoff² represented quinquivalent nitrogen by a cube, of which the nitrogen atom occupies the centre; the five bonds or valency directions being indicated by lines drawn from the centre to five corners of the cube. The linkages are all equal in length, but the angles which 1, 2, 3 make with 4 are smaller than with 5. Although these three linkages do not lie in one plane with the

¹ *Ber.*, 1889, 22, 40, 1172.

² *Ansichten über die org. Chem.*, 1878, 1, 80.

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nitrogen atom, being, according to van't Hoff, displaced by the influence of the acid radical 5, they are supposed to take up this position when the nitrogen becomes tervalent. The remaining two linkages 4, 5 lie along a diagonal of the cube (5 = acid radical).

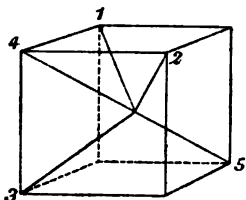


FIG. 21.

Willgerodt¹ suggests that the bonds of quinquevalent nitrogen are directed towards the summits of two superposed tetrahedra, represented by Fig. 22 or more simply by Fig. 23. The original valency directions

1, 2, 3 of the tervalent nitrogen are unaltered and lie in the plane

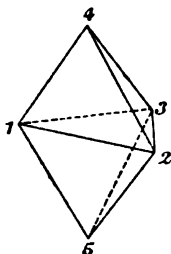


FIG. 22.

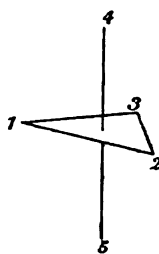


FIG. 23.

of the two contiguous faces of the double tetrahedron. The fourth and fifth groups (which include the acid radical) are attached to 4 and 5.

A third arrangement, that of a four-sided pyramid, in which nitrogen occupies the centre, has been proposed by Bischoff,² Fig. 24.

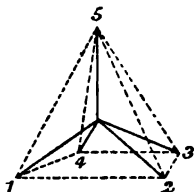


FIG. 24.

The acid radical is supposed to occupy the apex of the pyramid, and the other four radicals are grouped round the four corners of the square base. The pyramidal formula may be conveniently denoted by a plane projection of the following form :

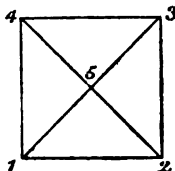


FIG. 25.

A difficulty arises in attempting to derive the pyramidal formula

¹ *Journ. prakt. Chem.*, 1890, 41, 291.

² *Ber.*, 1890, 23, 1971.

from a tervalent nitrogen group with three linkages in one plane without some alteration in the valency direction. But before discussing more fully the merits of the three formulae we will turn to the experimental data.

A quaternary ammonium salt of the formula Na_3bX may be formed in two ways, either from $\text{Na}_3 + \text{bX}$ or from $\text{Na}_3\text{b} + \text{aX}$.

The cube and double tetrahedron formulae, which may practically be considered as one, require that the two compounds should be isomeric,

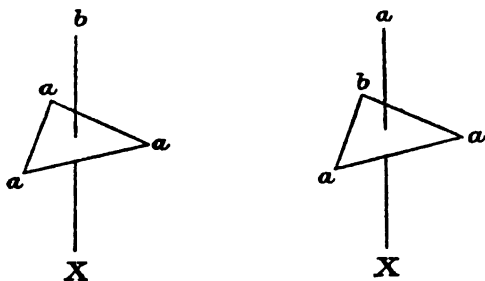


FIG. 26.

whereas the pyramidal formula demands that they should be identical.

The experimental evidence is somewhat conflicting. V. Meyer and Lecco¹ found that trimethylethylammonium iodide prepared from trimethylamine and ethyl iodide and from dimethylethylamine and methyl iodide were identical and not isomeric. Le Bel,² on the other hand, obtained two different crystalline chlorides and chloroplatinates of trimethylisobutylammonium by combining the radicals in a different order. In other cases, such as the chloroplatinate of benzyl triethylammonium, trimethylpropylammonium, trimethylethylammonium,³ &c., prepared in two different ways, no difference in crystalline form was observed. As the chlorides and chloroplatinates of primary and secondary amines, as well as of quaternary bases containing the same four radicals, frequently exhibit dimorphism in their salts, it is possible that the differences noticed by Le Bel are due to the same cause. A considerable number of experiments have been made in the attempt to

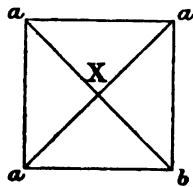


FIG. 27.

¹ *Ber.*, 1874, 7, 1747; 1875, 8, 288, 986.

² *Compt. rend.*, 1890, 110, 145; 1891, 112, 725; *Bull. Soc. Chim.*, 1890 (3), 4, 104.

³ Schryver and Collie, *Proc. Chem. Soc.*, 1891, 7, 89.

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obtain stereoisomers of the type Na_2bcX . The double tetrahedron requires three isomers, of which one is asymmetric and should yield optical enantiomorphs:

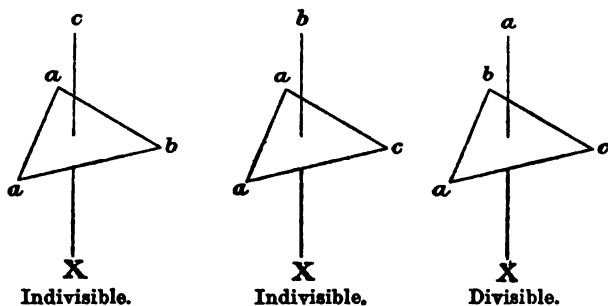


FIG. 28.

The pyramid formula should yield two isomers, one of which is asymmetric and divisible:

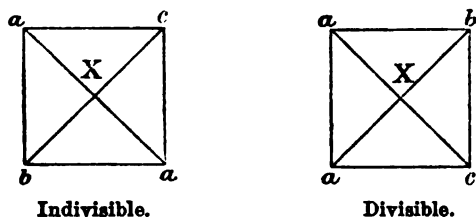


FIG. 29.

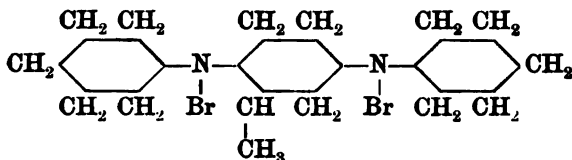
Among the first attempts to obtain quinquivalent compounds of this type are those of Schryver and Collie,¹ who succeeded in preparing dimethylethylisoamylammonium chloroplatinate by introducing the radicals in three different ways. When the process was conducted in the cold, two crystalline modifications—rhombic and monoclinic—were obtained. The monoclinic readily changes into the rhombic form on warming. As in the cases already described, there is no evidence that the phenomenon is not due to dimorphism.

A more comprehensive examination of this type of quaternary compound has been made by H. O. Jones,² who found that even when the combination of the tervalent group with the alkyl iodide was effected in the cold only one product was formed. This product could not be resolved into active enantiomorphs by Pope and Peachey's method (to be presently described in detail), which

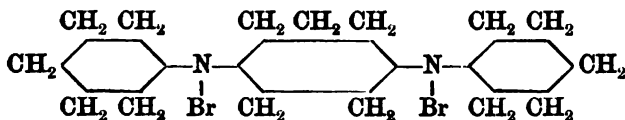
¹ *Proc. Chem. Soc.*, 1891, 7, 89.

² *Trans. Chem. Soc.*, 1903, 83, 1400.

consisted in recrystallizing the *d*-camphorsulphonate or *d*-bromocamphorsulphonate of the base. Other attempts in this direction by different observers¹ have been equally unsuccessful, with the exceptions of those of Aschan,² who obtained two isomers of ethylene-propylene-dipiperidinium dibromide, and also of ethylene-trimethylene-dipiperidinium dibromide and diiodide, by combining piperidine with alkylene bromides in two ways:



Ethylene-propylene-dipiperidinium dibromide.



Ethylene-trimethylene-dipiperidinium dibromide.

We come now to the type NabcdX, which on the whole affords the most interesting and conclusive results. The number of possible isomers is much increased. The double tetrahedron requires four, the pyramid three isomers, all of which are asymmetrical and should be divisible into optical enantiomorphs. Some of the first members of this type were obtained by Wedekind,³ who prepared phenyl-ethyl-methyl-allyl ammonium iodide in three ways. Nevertheless, only one product was obtained. The alleged difference between phenyl-benzyl-allyl-methyl ammonium iodide, obtained by the action of methyl iodide on benzyl-allyl-aniline, and that produced by combining allyl iodide with methyl-benzyl-aniline, or benzyl iodide with methyl-allyl-aniline, has now been traced to an error of observation, the first of the two being actually phenylbenzyltrimethyl ammonium iodide.⁴ Several other products which at first appeared dissimilar have since proved either to be identical or to have a different composition.⁵

The first successful attempt to resolve a compound of the type NabcdX into its enantiomorphs was made in 1891 by Le Bel⁶, who

¹ Menschutkin, *Zeit. phys. Chem.*, 1895, 17, 226; Evans, *Trans. Chem. Soc.*, 1897, 71, 522; Wedekind, *Ber.*, 1899, 32, 527.

² *Ber.*, 1899, 32, 988; *Zeit. phys. Chem.*, 1908, 46, 804.

³ *Ber.*, 1908, 36, 8791.

⁴ H. O. Jones, *Trans. Chem. Soc.*, 1905, 87, 1721.

⁵ *Ber.*, 1902, 35, 178.

⁶ *Compt. rend.*, 1891, 112, 724.

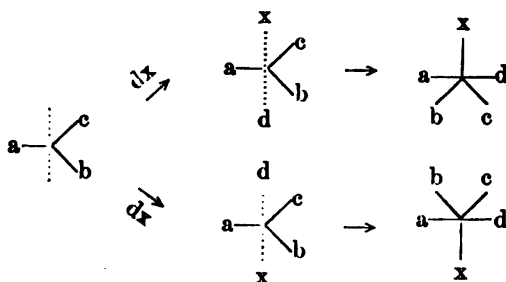
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submitted a solution of methyl-ethyl-propyl-isobutyl ammonium chloride to the action of the mould *penicillium glaucum*, when the solution became feebly laevo-rotatory, $\alpha_D = -7^\circ$ to -8° .

The active chloride was isolated as chloroaurate and chloroplatinate and analysed and converted into the acetate, which was also active, but the activity disappeared when the platinum or mercury double salt was decomposed by hydrogen sulphide. Doubt was thrown upon the result by Marcwald and Droste-Huelshoff, but it was reaffirmed by Le Bel, who announced that he had succeeded in preparing active solutions of other compounds by the same method. The results achieved by Pope and Peachey,¹ by Pope and Harvey,² and by H. O. Jones³ are of a much more decisive character. Pope and Peachey succeeded in resolving Wedekind's α -phenyl-benzyl-allyl-methyl ammonium iodide by converting it, by means of the silver salt, into the *d*-camphorsulphonate, and fractionally crystallizing the latter from acetone and ethyl acetate, solvents which prevent dissociation and therefore diminish the chances of optical inversion.

The two camphorsulphonates were then decomposed with potassium bromide and iodide and converted into the corresponding bromides and iodides of the base. The bromides showed a rotation of $[\alpha]_D = +64.1^\circ$ and -65.0° and the iodides of $\pm 56.8^\circ$ in chloroform solution.

The formation and configuration of quinquevalent nitrogen compounds have been placed in a clear light by H. O. Jones.⁴ Adopting Bischoff's pyramidal configuration as the most symmetrical and affording the smallest number of possible isomers, and further assuming the plane arrangement of tervalent nitrogen groups, the passage of tervalent to quinquevalent compounds is represented by the following scheme :



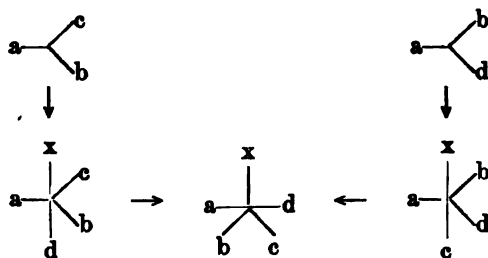
¹ *Trans. Chem. Soc.*, 1899, 75, 1127.

² *Trans. Chem. Soc.*, 1901, 79, 828.

³ *Trans. Chem. Soc.*, 1908, 83, 1400; 1904, 85, 223; 1905, 87, 135; see also Wedekind, *Ber.*, 1906, 38, 3933, and Scholtz, *Ber.*, 1905, 38, 595, 1289.

⁴ *Trans. Chem. Soc.*, 1905, 87, 1728.

The process represents an unstable intermediate stage which changes to the stable pyramidal form, and, by the addition of the groups dX in the two possible ways, gives enantiomorphous configurations. It is easy to explain also why the formation of the compound NabcdX from Nabc and dX, or from Nabd and cX, &c., should always give one product, since one arrangement there must be more stable than the others, and equilibrium would be established in this position during the intramolecular change. Considering only one of the enantiomorphs, the process would probably take place as follows:



It is easy to understand also, from this point of view, the absence of isomers of the type Na_3bX or Na_2bcX , each of which may be supposed to assume an arrangement which does not admit of resolution into enantiomorphs. Using the projection formulae, in which the dotted lines denote the plane of symmetry, the arrangement will appear thus:

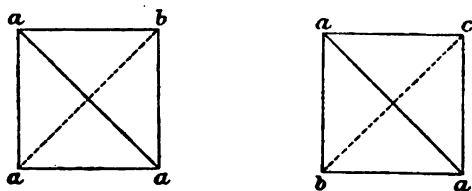


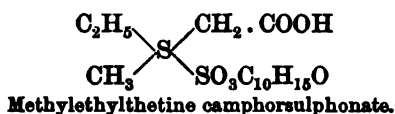
FIG. 30.

STEREOCHEMISTRY OF OTHER ELEMENTS

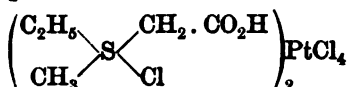
Optically Active Sulphur, Selenium, Tin, and Silicon Compounds. Pope and Peachey's discovery of optically active nitrogen compounds was soon followed by that of optically active sulphur, selenium, and tin compounds. The active sulphur compounds were obtained from methylethylthetine.¹ The bromide was decomposed by

¹ *Trans. Chem. Soc.*, 1900, 77, 1072.

silver *d*-camphorsulphonate, and the salts so obtained repeatedly crystallized from alcohol and ether.

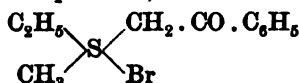


A fraction was obtained which melted at 118–120° and showed a rotation of $[\text{M}]_D = +68^\circ$, whereas that of the *d*-camphorsulphonic acid is $[\text{M}]_D = +52^\circ$. With the *d*-bromocamphorsulphonate the fraction melted at 166–168°, and gave a rotation $[\text{M}]_D = +290^\circ$ instead of $[\text{M}]_D = 275^\circ$, the rotation of the acid. The salt was decomposed by platinic chloride in an alcoholic solution containing hydrochloric acid, and yielded a platinum salt,



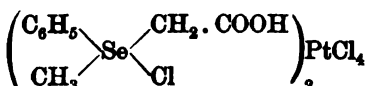
which gave a rotation of $[\text{M}]_D = +80.8^\circ$.

About the same time Smiles¹ obtained the methylethyl sulphine compound of *o*-bromacetophenone,



which he succeeded in resolving into its active enantiomorphs by Pope and Peachey's method of crystallization of the *d*-bromocamphorsulphonate. The *l*-compound is less soluble than the *d*-enantiomorph and separates out first. From the alcoholic solution the sulphines were precipitated as picrates, and showed a rotation in acetone solution of -9.2° and $+8.1^\circ$. The observations have since been revised by Pope and Neville, who obtained much higher rotations.

Active selenium compounds were obtained by Pope and Neville² from phenylmethyl selenetine bromide, which was converted into the *d*-bromocamphorsulphonate and submitted to fractional crystallization. Two salts were obtained melting at 168° and 151°, which, when converted into the chloroplatinates, showed a rotation of $[\text{M}]_D = +55^\circ$ and -54.3° in acetone solution.

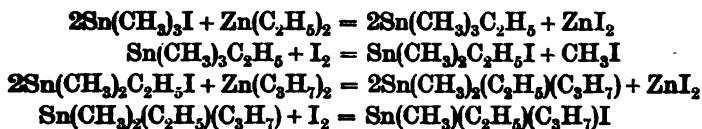


From both *d*-bromocamphorsulphonates mercuric iodide gave the same inactive mercuric iodide double salt, and precipitation with potassium mercuric iodide also produced racemisation.

¹ *Trans. Chem. Soc.*, 1900, 77, 1174.

² *Proc. Chem. Soc.*, 1902, 18, 198.

Active tin compounds were obtained by Pope and Peachey¹ by the method of Cahours and Ladenburg by the following series of reactions:



The product is an oil which boils at 270°. With silver *d*-camphor-sulphonate it yields the corresponding salt, which, after fractional crystallization, melts at 126°. It shows a rotation in dilute solution of $[\text{M}]_D = +95^\circ$, which corresponds to a rotation of $[\text{M}]_D = +45^\circ$ for the radical $\text{Sn}(\text{CH}_3)(\text{C}_2\text{H}_5)(\text{C}_3\text{H}_7)$.

Potassium iodide precipitates the iodide of the tin compound from a solution of the *d*-camphorsulphonate as an oil, which shows an unaccountable variation in rotatory power, the highest observed rotation being $[\alpha]_D = +23^\circ$ in ethereal solution.

The solution of the *d*-camphorsulphonate exhibits a remarkable phenomenon on evaporation, depositing only the *d*-salt and none of the *l*-salt. This is accounted for by the rapid racemisation of the *l*-salt, in consequence of which the less soluble *d*-salt, as it is deposited, is accompanied by a further racemisation of *l*-salt, until the whole is converted into dextro-salt. The salt of the *d*-bromocamphor-sulphonate showed a similar behaviour.

Various attempts to obtain active quinquivalent phosphorus and arsenic compounds have so far been unsuccessful. Iodonium com-

pounds of the formula $\begin{array}{c} \text{a} \\ \diagup \\ \text{I}-\text{X} \\ \diagdown \\ \text{b} \end{array}$ have also refused to separate into

active components, from which it is concluded that the three bonds, like those of tervalent nitrogen, lie in one plane with the iodine atom.² An asymmetric silicon compound of the formula:



has been prepared by Kipping,³ and has recently been resolved.

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- Lehrbuch der Stereochemie*, by A. Werner. Fischer, Jena, 1904.
Grundriss der Stereochemie, by A. Hantzsch. Barth, Leipzig, 1904.
Die Stereochemie des Stickstoffs, by W. van Ryn. Speidel, Zürich, 1897.
Zur Stereochemie des fünfwerthigen Stickstoffs, by E. Wedekind. Veit, Leipzig, 1899.
Die Entwicklung der Stereochemie, by K. Auwers. Winter, Heidelberg, 1890.
Brit. Assoc. Reports, 1904, p. 170, by H. O. Jones.

¹ *Proc. Chem. Soc.*, 1900, 16, 42, 116.

² *Trans. Chem. Soc.*, 1902, 81, 1850.

³ *Proc. Chem. Soc.*, 1904, 20, 15; 1907, 23, 9.

CHAPTER V

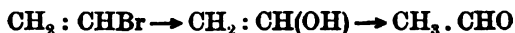
ISOMERIC CHANGE

ALTHOUGH our views on isomerism have of late years received a much wider interpretation than formerly owing to the recognition of the space arrangement of atoms, experience has taught us that among some classes of compounds structural isomerism is subject to certain limitations which were not foreseen by the original theory.

For example, attempts to prepare propylene alcohol from β -bromopropylene by the usual methods always result in the production of acetone:

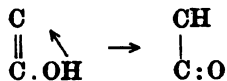


and in the same way vinyl bromide invariably yields acetaldehyde instead of the isomeric alcohol:¹



This result appeared so general that Erlenmeyer,² who carefully studied the reaction, concluded that 'all secondary alcohols in which two bonds of the radical are saturated by two bonds of a carbon atom are transformed at the moment of their formation into the aldehyde, &c.'

The change may be represented by the transference of a hydrogen atom from the oxygen to the carbon:



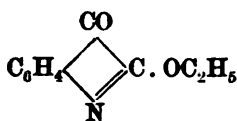
The same idea was utilized by Baeyer to explain the non-existence of the second isomer of isatin.³ Baeyer obtained two ethyl isatins, one of which gave potassium isatin on hydrolysis (alcohol being at the same time removed), and the other the potassium salt of ethylaminophenylglyoxalic acid. They were termed respectively

¹ *Annalen*, 1878, 192, 119.

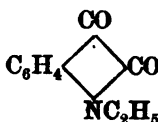
² *Ber.*, 1883, 16, 2183.

³ *Ber.*, 1880, 13, 309.

ethyl isatin and ethyl pseudoisatin, and were distinguished as the *normal* or *lactim* form and the *pseudo* or *lactam* form :

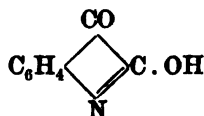


Ethyl isatin (*lactim*).



Ethyl pseudoisatin (*lactam*).

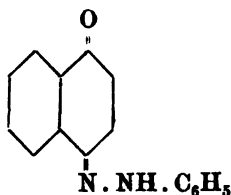
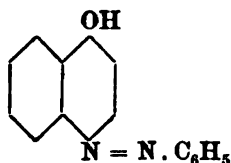
There is, however, only one isatin, to which Baeyer somewhat arbitrarily assigned the formula :



The non-existence of the second or pseudo form was accounted for by the wandering of the hydrogen atom from the nitrogen to the more stable position beside the oxygen atom.

Tautomerism. In a paper 'Ueber die Möglichkeit mehrerer Strukturformeln für dieselbe chemische Verbindung' Laar¹ drew attention to the phenomenon of one substance doing duty for two structural isomers and proposed for it the name *tautomerism* (*ταύτόρ, the same; μέρος, a part*).²

He refers to the case of isatin ; to the identity of two substances which might be expected to possess different formulae, one of which is formed by the action of diazobenzene chloride on α -naphthol and the other by that of phenylhydrazine on α -naphthaquinone ;

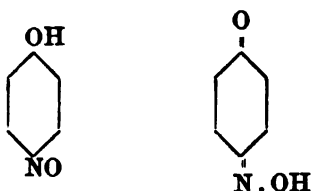


also to the twofold character of nitrosophenol or quinoneoxime, which on the one hand behaves like a phenol and gives nitrophenol and

¹ Ber., 1895, 18, 648.

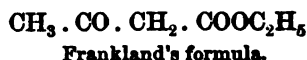
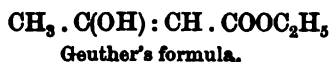
² Various other names, such as *pseudomerism*, *merotropism*, *desmotropism*, *tropomerism*, have been applied to the same or a similar phenomenon.

aminophenol by oxidation or reduction, and on the other is converted by hydroxylamine into a dioxime after the manner of a ketone.



He also discusses the structure of acetoacetic ester, which has now become the classical example of tautomerism.

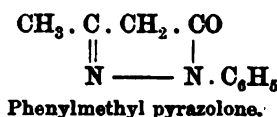
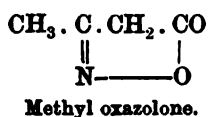
The question as to whether acetoacetic ester should be represented by Geuther's formula as β -hydroxycrotonic ester or by Frankland's formula as a ketone has been one of the long-debated problems of organic chemistry.



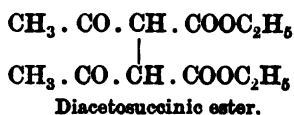
The evidence, which is derived from its chemical behaviour, will be seen to be very conflicting. The facts adduced in favour of Frankland's formula are as follows :

Acetoacetic ester with its alkyl derivatives is decomposed by dilute alkalis into acetone or its homologues ; nitrous acid converts it into isonitroso acetone ; it gives the usual reactions for ketones, forming hydroxybutyric acid on reduction and yielding additive compounds with hydrogen cyanide and sodium bisulphite.

Moreover, it combines with hydroxylamine to form β -oximino-butyric ester, and with phenylhydrazine to form a hydrazone, both of which lose alcohol and pass into their respective anhydrides, methyl oxazolone and phenylmethyl pyrazolone.



By the action of iodine on the sodium compound diacetosuccinic ester is formed, although it has since been shown that this is not the only product of the reaction (p. 192).



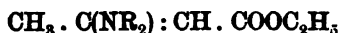
Again, acetic anhydride yields so small a quantity of an acetyl

derivative that the presence of a hydroxyl group seems very improbable, whereas acetyl chloride acting upon the sodium compound of the ester gives mainly diacetoacetic ester. Finally, Claisen has shown that the behaviour of acetoacetic ester is different from that of certain unsaturated alcohols of the type of Geuther's formula which readily react with acetic anhydride, &c. (p. 288).

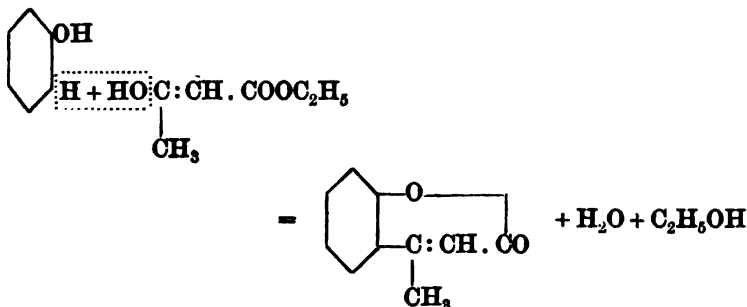
One fact which is strongly in favour of Geuther's formula is the acidic character of the ester, which enables it to form a sodium salt, a well-defined and crystalline copper salt and a violet coloured ferric salt. Although it is true that acetylene forms metallic derivatives in which the metal is associated with carbon, it is not very probable that this will occur when the much more electronegative oxygen is available for salt formation. Again, the action of chloroformic ester on the sodium compound, instead of yielding wholly acetyl malonic ester, gives mainly a carbonic ester of the formula¹:



and although, as previously stated, acetyl chloride acting on the sodium compound gives diacetoacetic ester, if the acid chloride and the ester react in presence of pyridine, the acetyl derivative of hydroxycrotonic ester is formed.² Furthermore, ammonia and amines yield amino and alkylamino crotonic esters of the general formula:



The union of acetoacetic ester with other organic compounds in which water is eliminated is often more simply represented by the hydroxyl than the ketone formula, as, for example, the formation of methyl-coumarin from phenol³:

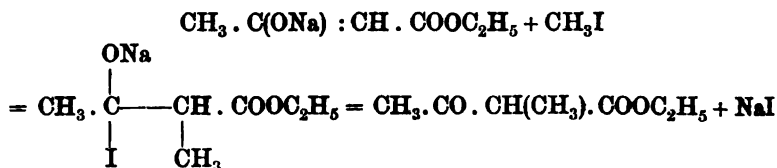


¹ Michael, *J. prakt. Chem.*, 1888 (2), 37, 478; 1891, 45, 580; 1892, 46, 189.

² Claisen, *Ber.*, 1888, 21, 8597, 8567; 1892, 25, 1760; Claisen and Haase, *Ber.*, 1900, 33, 1242, 8778.

³ V. Fechner and Duisberg, *Ber.*, 1888, 16, 2119.

Although the alkyl groups, which are introduced by the action of alkyl iodides and acetyl chloride on the sodium compound of acetoacetic ester, attach themselves to the carbon of the methylene group, the reaction does not necessarily imply a ketonic structure of the sodium compound, for, as Michael has suggested, it may be represented equally well by the following scheme,¹ in which an additive compound with the alkyl iodide is first formed and is succeeded by the separation of sodium iodide :



These are some of the arguments which have been advanced in support of the two formulae. It is now generally conceded, for reasons which will be discussed presently, that whilst free acetoacetic ester consists mainly of the ketonic form, the solid sodium compound must be represented by the isomeric β -hydroxycrotonic ester.

Since Laar drew attention to the subject in 1885 cases of tautomerism have rapidly multiplied. Before discussing the later development of the subject a short account will be given of a few of the principal types of tautomeric compounds, that is to say, compounds which possess a double function, but are commonly represented by only one substance.

If we examine the examples of tautomerism which have been given, we shall find that the structure of the compounds is such that it allows of the formation of isomers by the transference of a hydrogen atom from one polyvalent element to another, accompanied by a corresponding change in the linkages. This structure depends, therefore, on the presence of certain groups.

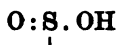
A convenient plan of classifying the greater number of tautomeric compounds has been proposed by Laar, who divides them into *dyads*, consisting of two polyvalent elements linked together, from one to the other of which the hydrogen atom may be supposed to travel; *triads*, in which the original two polyvalent elements are separated by a third (which is of necessity at least trivalent), so that the hydrogen has now to travel from the first to the third element in the chain, and so forth.

¹ Michael, *J. prakt. Chem.*, 1888, 37, 487; 1892, 46, 205; 1899, 60, 316.

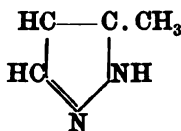
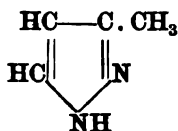
Dyads. Hydrogen cyanide may be taken as representative of a dyad group and its structure denoted by one of the following formulae:



For whilst only one hydrogen cyanide is known, there are two series of alkyl derivatives, the cyanides or nitriles and the isocyanides or carbamines. The sulphinic acids or sulphones are also dyads, for the one substance forms two series of compounds¹ derived from the two forms:

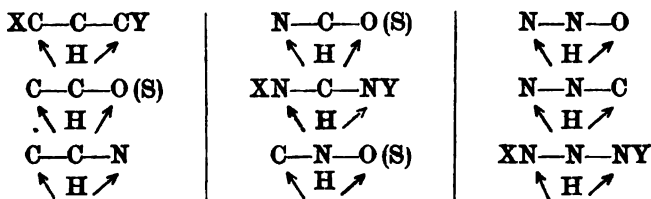


Methyl-pyrazole, described on p. 187, may also be included in the class of dyads, for the one compound gives rise to two N-phenyl derivatives and must be represented by the formulae²:



Methyl-pyrazole.

Triads. The following are the common types of triad grouping, in which the central atom of the triad is carbon or nitrogen and the end atoms carbon, nitrogen, oxygen or sulphur. These types furnish the most numerous and familiar examples of tautomerism. The symbols X and Y stand for radicals and (S) for sulphur.



Only the more important examples of the above types will be described.

Unsaturated Hydrocarbon Type. The type may be formulated thus:



This form of change is not, as a rule, included among examples of tautomerism for the reason that both isomeric forms are usually

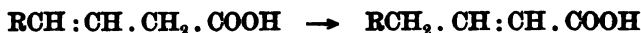
¹ Otto and Böseing, *Ber.*, 1892, 25, 230.

² Knorr, *Annalen*, 1894, 279, 192.

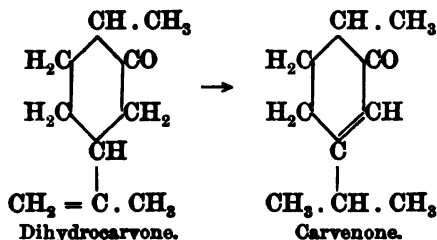
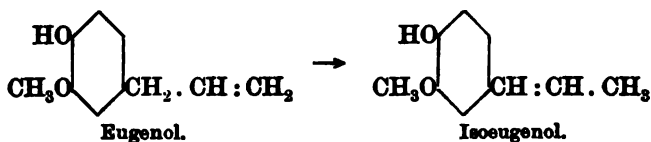
stable substances and can be easily isolated, whereas the original conception of tautomerism was associated with one substance forming two derivatives. The interconversion of the isodibutylenes described by Butlerow¹ and discussed on p. 208 is one example of this change.



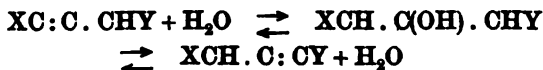
The conversion in hot alkaline solution of $\beta\gamma$ unsaturated acids into $\alpha\beta$ unsaturated acids observed by Fittig² and others furnishes another example (p. 458).



Other cases of the same kind are the conversion of β - into α -phenylpropylene, of eugenol into isoeugenol, of dihydrocarvone into carvenone, &c.



The above changes, which for convenience may be described as tautomeric, have in certain cases been shown to be reversible,³ and are usually ascribed to the intervention of water which is alternately added and removed (p. 204).



It should be recognized that this type may furnish cases of real tautomerism like benzene, as formulated by Kekulé, which yields only one instead of two ortho di-derivatives, or the glutamic acid of

¹ *Annalen*, 1877, 189, 76.

² *Ber.*, 1891, 24, 82; 1894, 27, 2677; *Annalen*, 1894, 283, 129; 1896, 299, 1.

³ *Annalen*, 1894, 283, 47.

Thorpe,¹ the $\alpha\beta$ and $\beta\gamma$ dimethyl derivatives of which are not isomeric but identical (p. 208).

Keto-Enol Type. This type includes acetoacetic ester and most of the more carefully studied examples of tautomerism. The two forms may be represented by the general scheme :

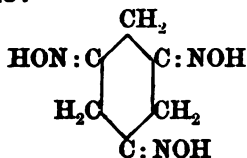


In accordance with a suggestion of Brühl the one is called the *keto form* and the other the *enol form*. The number of examples of this type is very large and embraces the 1.8 diketones like acetyl-acetone $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_3$, the β aldehydic and ketonic esters, like formyl and acetoacetic ester, and substances like malonic and cyanoacetic ester,² the sodium salts of which are probably represented by the formulae :

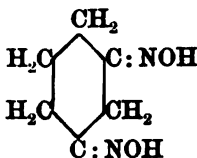


It also includes numerous cyclic compounds like phloroglucinol,³ dihydroresorcinol,⁴ succino-succinic ester,⁵ phenanthrone,⁶ and camphor,⁷ which function both as phenols and ketones.

Thus, phloroglucinol yields a trioxime and dihydroresorcinol a dioxime :

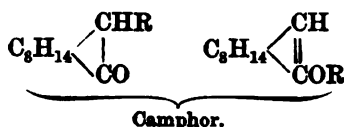
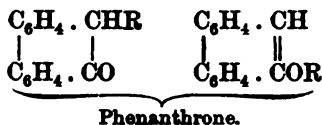


Phloroglucinol-trioxime.



Dihydroresorcinol-dioxime.

whereas phenanthrone and camphor form derivatives of both the ketonic and enolic type :



¹ Trans. Chem. Soc., 1905, 87, 1669. ² Thorpe, Trans. Chem. Soc., 1900, 77, 928.

³ Baeyer, Ber., 1885, 18, 2454; 1891, 24, 2687.

⁴ Merling, Annalen, 1893, 278, 20.

⁵ Baeyer, Ber., 1889, 22, 2168.

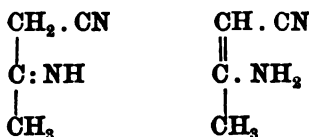
⁶ Japp and Findlay, Trans. Chem. Soc., 1897, 71, 1115.

⁷ Forster, Trans. Chem. Soc., 1901, 79, 987.

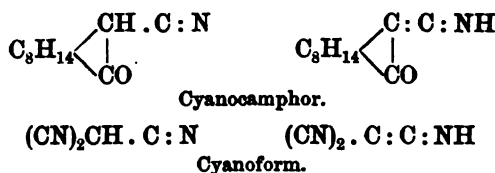
Cyanide-Imide Type. Examples of the third type on the list (p. 177) are not numerous :



but E. von Meyer's¹ diacetonitrile which exists in two modifications may, if it is not a case of geometrical isomerism, represent one :



and cyanocamphor and cyanoform² others :



Here again both isomers are known and the change from one to the other is reversible.

Amide-Imidol Type. Substances like isatin also belong to the triads, of which the two structures may be denoted by the general formulae :



They are usually distinguished as amide and imidol or normal and pseudo forms, or in the case of cyclic structures as lactam and lactim forms. The earliest examples of this class are isatin, indoxyl, and oxindol, which form stable derivatives of both types, but in the free state are represented by only one substance. The simple amides have similar properties. They have been studied by Tafel and Enoch,³ Comstock⁴ and Claisen.⁵ For example, the silver salts of formanilide and benzamide when treated with ethyl iodide yield ethyl derivatives which are isomeric with the compounds obtained in a similar manner from the sodium salts.

As the latter yield the ethyl derivative of the amine on hydrolysis they will possess the amide structure, those from the silver salt the imidol structure.

¹ *J. prakt. Chem.*, 1896, 52, 88.

² Hantzsch and Osswald, *Ber.*, 1899, 32, 641.

³ *Ber.*, 1890, 23, 1550.

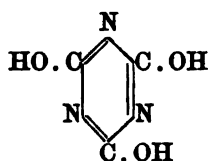
⁴ *Annalen*, 1896, 287, 361.

⁵ *Amer. Chem. J.*, 1892, 13, 514.

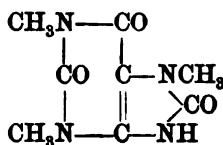
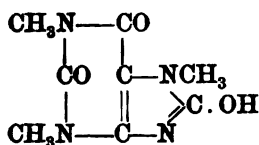
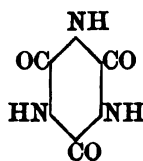
	From the sodium salt.	From the silver salt.
Ethyl benzamide . .	$C_6H_5CO \cdot NHC_2H_5$	$C_6H_5C(OC_2H_5) : NH$
Ethyl formanilide .	$C_6H_5N(C_2H_5) \cdot CHO$	$C_6H_5N : CH(OC_2H_5)$

It would be natural to conclude that in the sodium salts the metal is attached to nitrogen, and in the silver salts to oxygen; but if alkyl substitution takes place by addition of alkyl iodide, as Michael suggested in the case of acetoacetic ester (p. 176), it is not necessarily the case. The observations of Lander¹ on the simultaneous production of both alkyl derivatives by the action of alkyl iodide on the silver compound, or by the combined action of alkyl iodide and silver oxide, make it probable that both silver compounds are present.²

There are numerous cyclic compounds which exhibit a similar behaviour to the amides. Familiar examples are cyanuric acid and hydroxycaffeine, which exist as single substances, but yield two series of isomeric esters derived from the following structural forms:

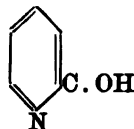
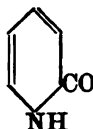


Cyanuric acid.



Hydroxycaffeine.

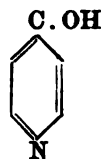
Examples might be multiplied.³ To the same type also belong the α - and γ -hydroxy derivatives of pyridine, which react both as hydroxypyridines and pyridones, and form two series of alkyl derivatives.

 α -Hydroxypyridine or α -Pyridone.

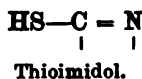
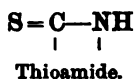
¹ *Trans. Chem. Soc.*, 1903, 83, 418.

² Titherley, *Trans. Chem. Soc.*, 1897, 71, 468; 1901, 79, 407.

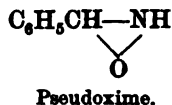
³ Marckwald, *Ber.*, 1892, 25, 2854; Dixon, *Trans. Chem. Soc.*, 1899, 75, 875.

 γ -Hydroxypyridine or γ -Pyridone.

Thioamide-Thioimidel Type. The thioamides, both in open chain and cyclic structures, commonly exhibit tautomerism like the amides,¹ and in some cases both isomeric forms are known.²



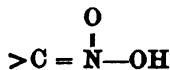
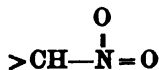
Oxime-Pseudoxime Type. Many oximes are known in two stereoisomeric forms; but in addition they occasionally exhibit tautomerism. Thus, each of the benzaldoximes forms two series of alkyl derivatives corresponding to different structural formulae:



which are distinguished as oxime and pseudoxime ethers. They have been studied by Luxmoore,³ who succeeded in preparing both ethers from syn- and anti-aldoxime (p. 189). Tautomerism has also been observed among nitroso compounds, which are sometimes interconvertible with aldoximes.⁴



Nitro-Pseudonitro Type. Tautomerism is represented by the two forms:



Hantzsch and Schultze⁵ found that the ordinary liquid phenylnitromethane dissolves in a solution of sodium hydroxide. From this solution acids precipitate in the cold a solid isomer, which gives a reddish-brown coloration with ferric chloride, and changes spon-

¹ Marckwald, *Ber.*, 1896, 29, 2920.² Hugerahoff, *Ber.*, 1899, 32, 3649.³ *Trans. Chem. Soc.*, 1896, 69, 177; see also Dunstan and Goulding, *ibid.*, 1901, 79, 628; Whiteley, *ibid.*, 1903, 83, 24.⁴ Schmidt, *Ber.*, 1902, 35, 2323, 2336, 3727; Pilotz and Steinbock, *Ber.*, 1902, 35, 3114; Bamberger and Fensel, *Ber.*, 1903, 36, 57, 85.⁵ *Ber.*, 1896, 29, 699, 2251.

taneously into the liquid modification. The two isomers are represented by the following formulae:



Similar results have been obtained with other nitro compounds.¹

Nitrosamine-Diazo Type. The geometrical isomerism exhibited by the diazo-compounds has already been discussed (p. 160), but in addition the isomers are capable of undergoing tautomeric change of the triad type:



Schraube and Schmidt,² for example, showed that the stable sodium salt of *p*-nitrodiazobenzene and methyl iodide gives nitrophenylmethyl nitrosamine, whereas von Pechmann,³ by using the silver salt, obtained the isomeric nitrodiazobenzene methyl ether.



The case resembles very closely that of the two series of alkyl anilides (p. 181).

Azo-Hydrazone Type. This is another example of a triad type of tautomeric compound, and may be represented as possessing either a hydrazone or azo structure.



Reference has already been made to the fact that diazobenzene chloride and α -naphthol give the same product as that obtained by the action of phenylhydrazine on α -naphthaquinone (p. 178). R. Meyer⁴ has shown that the compound obtained by combining diazobenzene chloride with malonic ester and then hydrolysing the product is the same as that which is formed by the action of phenylhydrazine on mesoxalic acid, and it may therefore be formulated either as a hydrazone or azo-compound.



Whichever formula is selected, one reaction must involve a tautomeric change. The choice of the formula has been the subject of much dis-

¹ Konowaloff, *Ber.*, 1896, 29, 2193; Hantzsch, *Ber.*, 1899, 32, 607.

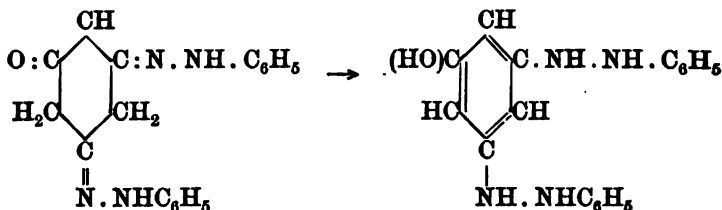
² *Ber.*, 1894, 27, 518.

³ *Ber.*, 1894, 27, 672.

⁴ *Ber.*, 1888, 21, 118; 1891, 24, 1241.

cussion, but the weight of evidence seems to be on the side of the hydrazone structure.¹ That the non-appearance of the second form is due to its instability seems probable from Fischer's observation² that azophenylethyl $C_6H_5N:N.C_2H_5$, which is prepared by the oxidation of symmetrical phenylethylhydrazine $C_6H_5NH.NHC_2H_5$ with mercuric oxide, is readily converted into the isomeric acetaldehyde phenylhydrazone by the action of mineral acids, and also, as Bamberger³ showed, by sodium ethoxide. The reverse change is produced by light.⁴

A tautomeric change of a somewhat different type has been studied by Baeyer,⁵ who brings evidence to show that the product of the action of phenylhydrazine on phloroglucinol and similar compounds is not a hydrazone of the keto form, but a hydrazide, and that tautomeric change is brought about by the wandering of a hydrogen atom from a carbon of the benzene nucleus to the nitrogen of the hydrazone radical, which he explains in the following way:



A similar case is that of the hydrazone of camphor quinone, which has been obtained by Betti⁶ in both isomeric forms.



Amidine Type. In this type of tautomeric compound the hydrogen is transferred from one nitrogen atom to another.



The simplest example is cyanamide, which has properties corresponding to both the formulae $\text{NH}_2.\text{C}:\text{N}$ and $\text{NH}:\text{C}:\text{NH}$.

Other examples are the amidines. By combining benzanilidoiminochloride with *p*-toluidine, von Pechmann⁷ obtained the same

¹ Japp and Klingemann, *Annalen*, 1888, 247, 190; Freer, *Amer. Chem. J.*, 1899, 21, 14; Thiele and Heuser, *Annalen*, 1896, 290, 1; Bülow and Ganghofer, *Ber.*, 1904, 37, 4169.

² *Annalen*, 1879, 199, 328; *Ber.*, 1896, 29, 793.

³ *Ber.*, 1903, 36, 56.

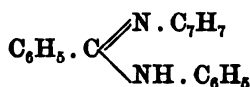
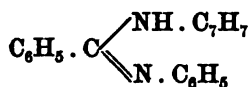
⁴ *Ber.*, 1891, 24, 2688.

⁵ Chattaway, *Proc. Chem. Soc.*, 1906, 22, 96.

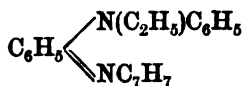
⁶ *Ber.*, 1899, 32, 1995; see also Lapworth, *Trans. Chem. Soc.*, 1902, 81, 1508.

⁷ *Ber.*, 1896, 28, 869, 2862.

product as that from benz-*p*-toluidiminochloride and aniline, instead of two different compounds of the formulae:

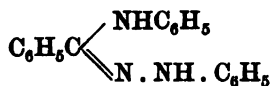
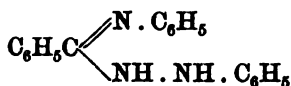


Although the same phenyl-*p*-tolylbenzamidine is produced in the two reactions, it nevertheless gives rise to two different ethyl derivatives of the formulae:



which von Pechmann identified by comparing them with the compounds obtained from the corresponding iminochlorides by the action of ethylaniline in one case and ethyl-*p*-toluidine in the other. In other cases only one alkyl derivative was obtained; methylnaphthylbenzamidine yields only one methyl derivative, from which von Pechmann concluded that tautomerism occurs only if the radicals are similar in character.

Among certain classes of amidine compounds both structural isomers are formed. Von Pechmann¹ succeeded in isolating both phenylanilbenzamidines from the product of the action of phenylhydrazine on benzanilideiminochloride,

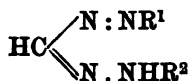
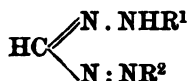


and Walther² has found as many as four isomeric compounds of the formula



some of which must represent geometrical as well as structural isomers.

Other examples of the same kind are the formazyl derivatives of von Pechmann³ and Wallach⁴ of the general formula:



and the guanidine compounds of Forster,⁵ Marekwald and Wolff,⁶

¹ Ber., 1895, 28, 2866.

² Ber., 1894, 27, 1679.

³ Annalen, 1875, 175, 85.

⁴ J. prakt. Chem., 1897, 55, 41.

⁵ Annalen, 1882, 214, 209; Ber., 1883, 16, 147.

⁶ Ber., 1892, 25, 3116.

and Huhn,¹ which are represented in each case by only one substance :



Very similar in character also are the nitroso-aldehydrazones of Bamberger and Pemsel,² which are very unstable, and pass spontaneously into the isomeric azoaloximes.



Nevertheless, in a few cases, both isomeric forms have been isolated.

Diazoamino Type. Tautomerism is exhibited by diazoamino compounds, which contain the triad group.



When diazobenzene chloride acts upon toluidine a different product would be anticipated from that produced by the action of diazotoluene chloride upon aniline.



Meldola and Streatfeild³ have proved that the compounds obtained in this way are not isomeric but identical.

Virtual and Functional Tautomerism. Where tautomerism is expressed by two structural forms denoting similar chemical properties, such as the amidine, formazyl, guanidine, and diazoamino types just described, von Pechmann employs the term *virtual* to distinguish it from *functional* tautomerism, in which the structure of the tautomeric forms expresses a difference of function, such as the tautomerism of the keto and enol, amide and imidol, nitroso and oxime compounds, and in fact the great majority of tautomeric compounds.

Tautomerism of Heterocyclic Compounds. The identity of the methyl pyrazoles obtained by Knorr⁴ from 1-phenyl 3-methyl-

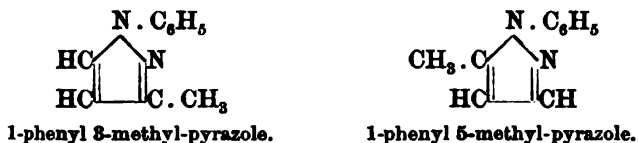
¹ Ber., 1886, 19, 2404.

² Ber., 1903, 36, 85.

³ Trans. Chem. Soc., 1887, 51, 102, 434; 1888, 53, 664; 1889, 55, 412; 1890, 57, 785.

⁴ Annalen, 1894, 279, 188.

and 1-phenyl 5-methyl-pyrazole, by removing the phenyl group, is a very interesting example of tautomerism.



The removal of the phenyl group would be expected to yield two structural isomers.



The existence of one substance can only be explained by the wandering of a hydrogen atom from one nitrogen atom to a more stable position beside the adjoining nitrogen atom, or, as Knorr has suggested, by the oscillation of the hydrogen atom between the two positions, which is practically synonymous with a mixture of the two forms. This view is supported by the fact that a mixture of two dimethyl pyrazoles is formed on methylation. The case is exactly parallel to the formation of two ethyl derivatives of phenyl-tolylbenzamidine (p. 185).

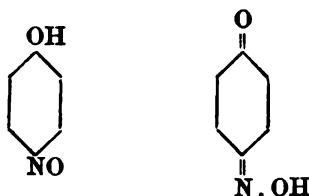
How complex cyclic tautomerism may become is seen from another case in which Knorr¹ obtained three methyl derivatives of phenyl methyl pyrazolone. They are regarded as derivatives of the following tautomeric forms:



Quinone Type. A typical example is the compound nitroso-phenol already referred to, which is obtained both by the action of nitrous acid on phenol and of hydroxylamine on quinone,² and may therefore be represented by two structural formulae:

¹ *Ber.*, 1895, 28, 706. See also Fischer and Rigaud, *Ber.*, 1901, 34, 4202; Thiele and Büchner, *Annalen*, 1906, 347, 258.

² Goldschmidt, *Ber.*, 1884, 17, 218.

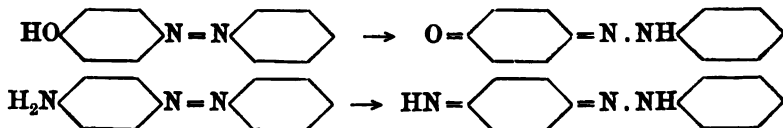


Nitrosophenol or Quinoneoxime.

It is customary to adopt the second of the two formulae, since the compound yields alkyl and acyl derivatives of the oxime type and a dioxime with hydroxylamine. Moreover, the green or blue colour, which is characteristic of true nitroso compounds, is absent.

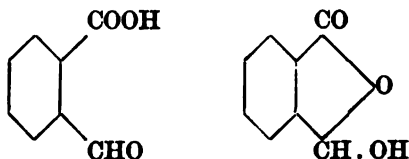
Both yellow and red modifications of oximes derived from orcinol and β -naphthol¹ have been described, but whether they represent the nitroso and oxime structure is uncertain.

The colour of the azo and other dyes is frequently referred to the quinonoid structure, which the hydroxy-azo and amino-azo compounds are supposed to assume by a process of tautomeric change.



The phenomenon of fluorescence is also ascribed to tautomerism of a special kind.²

Lactone Type. Lactone tautomerism is applied to cases of tautomerism where an interchange of atoms may occur between groups in the ortho or, in open chain-compounds, in the γ -position. Liebermann³ found that aldehydophthalic acid assumes the functions of a lactone or hydroxyphthalide (p. 330),



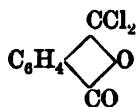
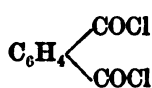
and it is well known that phthalyl chloride and *o*-sulphobenzoyl-dichloride behave in some cases as if both atoms of chlorine were

¹ Henrich, *Monatsh.*, 1897, 18, 142; Kehrman and Zimmerli, *Ber.*, 1898, 31, 2417.

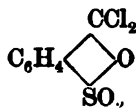
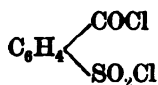
² Hewitt, *Proc. Chem. Soc.*, 1900, 16, 3.

³ *Ber.*, 1896, 29, 175, 2080.

attached to the same carbon.¹ Each compound must therefore be represented by two formulae :



Phthalyl chloride.



Sulphobenzoyl dichloride.

Dynamic Isomers or Desmotropic Compounds. It will be seen from the foregoing examples of tautomerism that Laar's conception of one substance representing two structural isomers has not been consistently adhered to, for several cases are cited in which both isomers anticipated by theory are known. The latter have been called *dynamic isomers* or sometimes *desmotropic compounds* to distinguish them from the single or tautomeric substance. Dynamic isomers differ in no respect from ordinary isomers but in the fact that they are more or less readily interconvertible. There is little doubt that this convertibility or metamorphosis of isomeric substances is the idea which Berzelius² had in mind when he introduced the term *metamerism*, although the example of cyanuric and cyanic acid, which he selected to illustrate it, is one, not of isomeric, but of polymeric change (p. 9).

Fresh light has been thrown on the subject of tautomerism by the discovery of both structural forms of the familiar and peculiarly labile (keto-enol) type of tautomeric compounds. Its immediate result has been to demonstrate the futility of the method hitherto adopted of attempting to ascertain the structural formula of a tautomeric compound from that of its derivatives or from the chemical behaviour of the compound itself. It has been shown that the extreme mobility of one or both of the isomers renders them liable to isomeric change, not only in presence of a reagent, but frequently by a rise of temperature or the mere action of a solvent.

It may thus happen that the lower melting isomer may fuse, and as the temperature rises may again solidify and remelt when the equilibrium temperature is reached. That point will not be, as

¹ Graebe, *Ber.*, 1888, 16, 860; Auger, *Ber.*, 1888, 21, Ref. 610; *Ber.*, 1891, 24, Ref. 819; Remsen, *Amer. Chem. J.*, 1896, 18, 792; List and Stein, *Ber.*, 1898, 31, 1648; R. Meyer, *Ber.*, 1895, 28, 1577.

² *Jahresb.*, 1832, 12, 68.

Claisen supposed, the true melting-point of the second isomer, but the fusion temperature of the equilibrium mixture (p. 200).

Both Claisen and von Pechmann had already pointed out the uncertainty of chemical reactions as indicative of structure. They adopted a method of comparison whereby they claimed to demonstrate by the behaviour of certain hydroxymethylene compounds, such as formylacetic ester, formylpropionic ester and hydroxymethylene camphor (see p. 283), that they are true hydroxyl compounds, partaking partly of the character of alcohols, partly of that of acids. As in no case do the substances in question exhibit the characteristics of the acetoacetic ester type of compound, they concluded that the latter has a ketonic and not an enolic structure.¹

Among the earliest examples of dynamic isomers are acetyldibenzoylmethane, tribenzoylmethane, and mesityloxide-oxalic ester discovered by Claisen.² The first two compounds were obtained by the action of benzoyl chloride on the sodium compounds of benzoylacetyl methane $C_6H_5CO \cdot CH_2 \cdot COCH_3$ and dibenzoylmethane $C_6H_5CO \cdot CH_2 \cdot COC_6H_5$, and the third by condensing mesityl oxide with oxalic ester in presence of sodium ethoxide. The following formulae, which are distinguished as 'enol' and 'keto', were assigned to the isomeric forms:

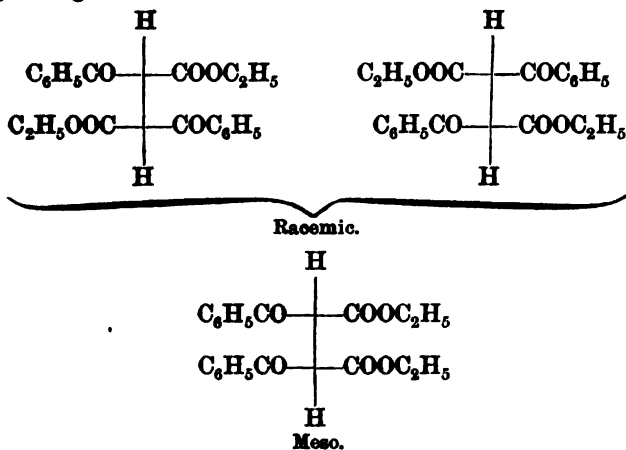
	Enol.	Keto.
Acetyldibenzoylmethane	$ \begin{array}{c} C(OH) \cdot CH_3 \\ \diagdown \\ C-CO \cdot C_6H_5 \\ \diagup \\ CO \cdot C_6H_5 \\ m. p. 80-85^\circ \end{array} $	$ \begin{array}{c} CO \cdot CH_3 \\ \diagdown \\ HC-CO \cdot C_6H_5 \\ \diagup \\ CO \cdot C_6H_5 \\ m. p. 107-110^\circ \end{array} $
Tribenzoylmethane	$ \begin{array}{c} C(OH) \cdot C_6H_5 \\ \diagdown \\ C-CO \cdot C_6H_5 \\ \diagup \\ CO \cdot C_6H_5 \\ \text{isomerises on melting} \end{array} $	$ \begin{array}{c} CO \cdot C_6H_5 \\ \diagdown \\ HC-CO \cdot C_6H_5 \\ \diagup \\ CO \cdot C_6H_5 \\ m. p. 222-226^\circ \end{array} $
Mesityloxide-oxalic ester	$ \begin{array}{c} CO \cdot CH : C(CH_3)_2 \\ \\ CH : C(OH) \cdot COOC_2H_5 \\ m. p. 21-22^\circ \end{array} $	$ \begin{array}{c} CO \cdot CH : C(CH_3)_2 \\ \\ CH_2 \cdot CO \cdot COOC_2H_5 \\ m. p. 59-60^\circ \end{array} $

The compound obtained by precipitating acetyldibenzoylmethane from its cold solution in sodium carbonate with acetic acid melts at $80-85^\circ$, dissolves in alkalis with a yellow colour, gives a dark red coloration with alcoholic ferric chloride, and forms a crystalline copper salt. It is known as the α -compound. When heated above

¹ Wislicenus, *Ber.*, 1887, 20, 2930; Claisen, *Ber.*, 1892, 25, 1776; von Pechmann, *Ber.*, 1892, 25, 1040.

² *Annalen*, 1893, 277, 184; 1896, 291, 25.

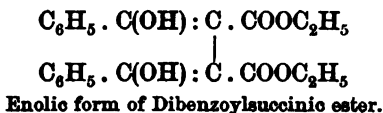
its melting-point it solidifies at about 90° and melts a second time at 110° . This is taken as indicative of a change into the second or β -form. The new substance is not directly dissolved by sodium carbonate, copper acetate produces no immediate precipitate, and the coloration with ferric chloride is only slowly developed. The first or α -compound which readily forms metallic salts is assumed to contain a hydroxyl group and consequently represents the enol form; the second or β -compound is the keto form. The change of enol to keto may also be effected by certain solvents. Ligroin and benzene are without action, but when heated with alcohol on the water-bath the solution is found to contain about one-third of the keto form; if dilute alcohol is used a still larger proportion is produced. The reverse change of keto to enol may be effected by adding alkali, when the keto compound passes gradually into solution, and on acidifying the well-cooled liquid with acetic acid the enol compound is precipitated. Similar observations have been made with tribenzoyl methane and mesityloxide-oxalic ester. The non-existence of enolic forms of triacetyl methane $\text{CH}(\text{COCH}_3)_3$ and benzoyldiacetyl methane $\text{CH}(\text{COCH}_3)_2\text{COC}_6\text{H}_5$ is accounted for by the more electropositive nature of the radicals.¹ This investigation was followed by many others on the same lines. Knorr² found that dibenzoylsuccinic ester, which is obtained by the action of iodine on sodium benzoyl-acetic ester, consists of two isomeric substances which could be separated by means of alcohol. As neither of them gave a coloration with ferric chloride, Knorr concluded that they were both ketonic, corresponding to the racemic and meso forms of tartaric acid.



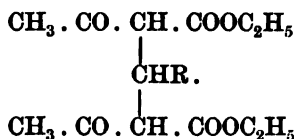
¹ Claisen, *Ber.*, 1892, 25, 1763; *Annalen*, 1893, 277, 206.

² *Annalen*, 1896, 293, 70.

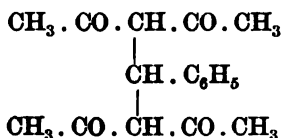
But if either of these compounds is dissolved in a solution of sodium ethoxide, and precipitated in the cold with dilute sulphuric acid, an oily product is obtained which gives the ferric chloride reaction, and unlike the other isomers dissolves in dilute alkalia. It is represented by the enolic formula :



On heating it passes into the two solid keto modifications. Similar results were obtained with diacetosuccinic ester by Knorr,¹ with alkylidenediaceetoacetic ester by Rabe²,



and with benzylidenediacetylacetone by Schiff,³ who claims to have



obtained no less than six structural or geometrical isomers.

A further insight into the mechanism of tautomeric change is afforded by W. Wislicenus' discovery of the desmotropic forms of formylphenylacetic ester :⁴



They are obtained by the condensation of formic ester with phenylacetic ester in presence of sodium (see p. 266). Both isomers are found in the product, and since one is a liquid and the other a solid they can be separated by filtration. If precipitated by carbon dioxide from alkaline solution the enol form is obtained, if by sulphuric acid the keto form is produced. The liquid or α -ester gives the usual reactions for the enol form with ferric chloride and copper acetate. The solid or β -ester, which melts at about 70°, gives no coloration with ferric chloride; and though it forms both sodium and copper compounds, they are very unstable and pass into the corresponding

¹ *Annalen*, 1896, 293, 86.

² *Annalen*, 1900, 313, 129; *Ber.*, 1899, 32, 84.

³ *Annalen*, 1899, 306, 332; 309, 206.

⁴ *Annalen*, 1896, 291, 147; *Ber.*, 1899, 32, 2387.

derivatives of the α -ester. Whilst both esters remain unchanged in closed vessels for an indefinite time, exposed to the air the β -ester soon becomes liquid, producing some of the α -form. This change is more quickly effected at 70° . On the other hand the α -ester changes slowly but almost completely into the β -compound at the ordinary temperature on introducing a crystal of the latter substance.

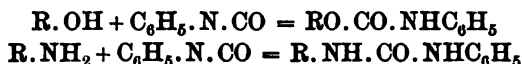
Perhaps the most interesting result of this investigation is the discovery that in certain solutions a condition of equilibrium is reached between the two forms which is dependent upon temperature, concentration and the nature of the solvent. The equilibrium point was ascertained by observing the intensity of the coloration with ferric chloride. If either α - or β -ester is dissolved in the same solvent, under the same conditions of temperature and concentration, the coloration produced by adding an alcoholic solution of ferric chloride to the one ester diminishes in intensity, whilst that of the other gradually increases until eventually the two solutions appear of the same tint. Wislicenus observed further that whilst alcohol and water favour the formation of the keto form, benzene favours that of the enol form, and he ascribed the effect, in accordance with a previous suggestion of Knorr,¹ to the ionizing power of the solvent. In the present case the more strongly ionizing solvent determines the keto formation. A very interesting confirmation of Wislicenus' results on the action of the solvent is afforded by the observations of Brühl.² He found that the dynamic isomers of Claisen's mesityloxide-oxalic ester showed well-marked differences in refractive and dispersive power, and was thus able, whilst avoiding the disturbing influences which might be introduced by the use of a chemical reagent, to follow the changes effected by the solvent. He found that chloroform had little action, whilst methyl and ethyl alcohol rapidly ketonize the dissolved enol form. Brühl, like Wislicenus, ascribed the change to the ionizing action of the solvent, which appeared also to be closely related to its dielectric constant. Without discussing at present the mechanism of the change, it is clear from the examples which have been given that the convertibility of dynamic isomers belongs to a class of reversible reactions of a peculiarly sensitive kind.

Determination of Structure, Chemical Methods. In view of the mobility of dynamic forms it may be well to consider to what extent chemical methods are available for determining structure. It

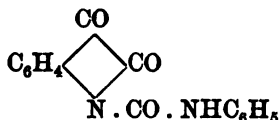
¹ *Ber.*, 1895, 25, 708.

² *Zeit. phys. Chem.*, 1899, 30, 1; *Ber.*, 1899, 32, 2826.

is evident that many reagents are excluded from the simple fact that they produce isomeric change, a fact which applies equally to the formation of derivatives of the compounds in question. There is scarcely one of the reactions, discussed at length on pp. 174, 175, and formerly used as evidence in favour of the keto or enol structure of acetoacetic ester, which has withstood the test of subsequent experience. It is on this account that the action of bases and acids is excluded, and also the derivatives which are obtained by their aid. It has been shown that sodium compounds are mainly enolic; but it does not follow that the derivative obtained by the use of the sodium compound is a guide to the structure of the original substance. For the same reason acetic anhydride cannot be employed to ascertain the presence of hydroxyl. Both forms of formylphenylacetic ester yield the same acetyl derivative. Acid chlorides act in the same way. Many ketones are known to yield enolic acyl derivatives. Phenyl hydrazine and hydroxylamine are also excluded. Here again both isomers of formylphenylacetic ester give the same hydrazone and oxime. Among the few reagents which appear to have little effect upon the isomers is phenyl carbimide dissolved in a non-ionizing solvent. It reacts in the cold with hydroxy- and amino-compounds in the following way to form carbamic esters and carbamido compounds:



Isatin, for example, forms a carbamino derivative, and is therefore a lactam and not a lactim as Baeyer supposed.



Phenyl carbimide combines with phloroglucinol, but not with succino-succinic ester, indicating that the former is enolic and the latter ketonic.

An alcoholic solution of ferric chloride can also be used to determine the presence of the enolic form, and, as already pointed out, to follow the changes taking place between the two dynamic isomers. In other cases, however, it acts as a catalyst, and Lowry¹ has shown that equilibrium is established instantly between the dynamic isomers of π -bromonitro-camphor on the addition of this reagent.

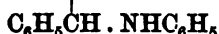
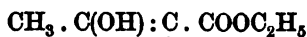
To determine the presence of keto and enol form in acetoacetic

¹ *Trans. Chem. Soc.*, 1899, 75, 280.

ester Schiff¹ conceived the device of bringing about a combination between the ester and a compound with which either enol or keto form will readily unite. The substance selected was benzalaniline $C_6H_5CH:N.C_6H_5$, which can combine with acetoacetic ester in the following ways:



In union with the *keto* form.



In union with the *enol* form.

A product was obtained melting at 95° , which was shown to be a mixture of the two forms. The individual substances were obtained separately either by adding to the mixture of acetoacetic ester and the reagent a few drops of piperidine, which ketonizes the ester, or a trace of sodium ethoxide, which converts it into the enol form. These two compounds melt at 78° and 104° respectively. Similar results have been obtained with benzoylactic ester, and, by Francis,² with dibenzyl ketone and desoxybenzoin. The action of piperidine and sodium ethoxide is interesting. The small amount of reagent required led Schiff to infer that the action is catalytic. This view is clearly opposed to the general conception of a catalytic agent which can only accelerate equilibrium but not modify the proportions of the ultimate constituents. It is, moreover, contradicted, as Schaum³ has pointed out, on thermodynamical grounds as well as by his own experimental evidence. He showed that, by the displacement of equilibrium without adding energy to a system, one change is accelerated at the expense of the other, and consequently a certain amount of energy is used. If the catalyst is then removed, the original equilibrium is restored, and the energy set free can be utilized to perform work, so that by combining the two systems a perpetual motion is created. Experimentally he proved that neither reagent affects in the slightest degree the density or specific refraction when equilibrium is established. An explanation of the process has been given by Lowry.⁴ He suggests that each reagent reacts with one form only, producing an additive compound, which then interacts with the benzalaniline, and at the same time liberates the reagent. One of the isomers is thus removed from the mixture, equilibrium is restored, to be again disturbed by the reagent, and so the process continues until the whole undergoes change into the one product.

¹ Ber., 1898, 31, 205, 601, 1304, 1888; 1899, 32, 832.

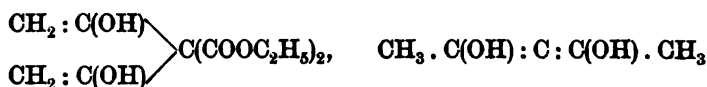
² Trans. Chem. Soc., 1899, 75, 865; Ber., 1908, 36, 987; Trans. Chem. Soc., 1904, 87, 998.

³ Ber., 1898, 31, 1964.

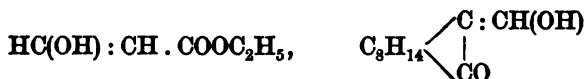
⁴ Trans. Chem. Soc., 1899, 75, 241.

Physical Methods have afforded much more valuable information about isomeric change than the chemical reactions referred to. The methods utilized include density, optical properties, electrical conductivity, solubility, colour, &c.

Refraction and Dispersion. Brühl¹ has shown that molecular refraction and dispersion offer an excellent means of differentiating the enol and keto forms, and has determined the structure of a variety of compounds in this way. According to Brühl free acetoacetic ester represents the keto form, whilst its sodium compound is enolic.² In other respects Claisen's rule that negative groups favour the enol formation is fully confirmed. Oxalacetic ester and acetylmalonic ester are enolic compounds, whilst diacetylmalonic ester and acetylacetone, &c., have a di-enolic structure.



And in addition, formylacetic ester and hydroxymethylene-camphor were shown to belong to the enolic type.



Magnetic Rotation. The results derived by W. H. Perkin³ from observations of the magnetic rotation of acetoacetic ester and other ketones agree substantially with those of Brühl. Acetoacetic ester is a ketone, acetylacetone is probably a mixture of 80 per cent. mono- and 70 per cent. di-enol, whilst ethylacetylacetone is mainly ketonic, from which it follows that the positive ethyl radical favours the ketonic structure and thus in a sense supports Claisen's rule (p. 191). The further interesting observation was made that those ketonic compounds which exhibit enolic structure are rendered more ketonic with rise of temperature, in other words, that the condition of equilibrium between the isomers changes with the temperature.

Electrical Conductivity. An interesting application of the ionization hypothesis to the study of tautomeric change has been elaborated by Hantzsch.⁴

In 1896 Hantzsch and Schultze⁵ obtained the two dynamic isomers

¹ *Ber.*, 1892, 25, 366; *J. prakt. Chem.*, 1894, 50, 159; *Zeit. phys. Chem.*, 1900, 34, 81.

² Brühl and Schröder, *Zeit. phys. Chem.*, 1904, 50, 1; 1905, 51, 1.

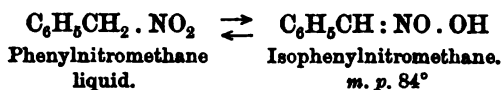
³ *Trans. Chem. Soc.*, 1892, 61, 800.

⁴ *Ber.*, 1899, 32, 575, 8066.

⁵ *Ber.*, 1896, 29, 699, 2251.

of phenylnitromethane $C_6H_5CH_2NO_2$ (see p. 182). The product obtained by the action of silver nitrate on benzyl iodide is an oil which dissolves in soda solution and forms a sodium salt, from which hydrochloric acid precipitates in the cold a crystalline substance which melts at 84° . The latter, in contact with acids, passes gradually into the oily isomer, and the same thing occurs on warming the substance in ethereal or alcoholic solution. The two may be distinguished by the intense brown coloration which alcoholic ferric chloride gives with the crystalline modification.

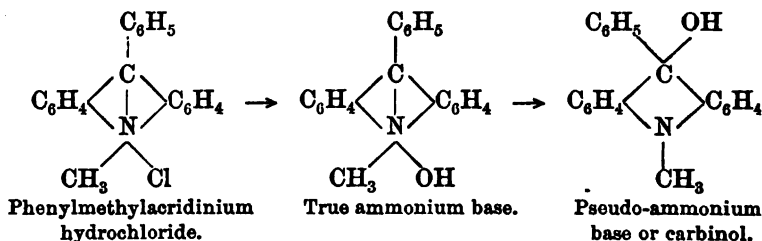
The conversion of the one isomer into the other is explained by a tautomeric change of the following nature:



Whereas the liquid compound is a neutral substance and a non-electrolyte, the isomer is a strong acid and an electrolyte. The presence of the second compound and its gradual change into the first may therefore be recognized by its decreasing conductivity in solution, whilst the passage of the first into the second may be followed by observing the gradual neutralization of the solution on the addition of an alkali. These and other manifestations of tautomerism, such as the colour change of the liquid on the addition of an alkali, may be observed in compounds like the aliphatic and aromatic nitro-compounds, nitroparaffins, nitrophenols, and nitrolic acids, lactams, primary nitrosamines, oximinoketones, e.g. violuric acid, quinoximes, &c., which are unknown in desmotropic forms, owing, as a rule, to the instability of the free enol type. Such compounds have been named by Hantzsch *pseudo-acids*, by which term is implied the free compounds, which, not being acids themselves, exhibit by a change of structure the characteristic behaviour of acids, and the manifestation is termed *ionic isomerism*. Hantzsch also recognizes a group of basic substances corresponding to pseudo-acids which he terms *pseudo-ammonium bases*.¹ These substances are not in themselves bases, but exhibit ionic isomerism, inasmuch as they pass into true ammonium salts on the addition of an acid and thereby become strong electrolytes. Like the pseudo-acids they also show colour changes and 'abnormal neutrality'. These changes were first studied in the case of phenylmethylnitroacridinium chloride. The addition to an aqueous solution of the salt of an alkali or silver oxide sufficient to unite with the acid liberates a strong base, which

¹ Ber., 1899, 32, 594, 8109, 8132; 1900, 33, 278.

shows a degree of dissociation comparable with that of potassium hydroxide. Its conductivity then gradually diminishes until it reaches zero, and at the same time the solution becomes neutral and the pseudo-base is precipitated. The change is represented by the wandering of the hydroxyl ion to the carbon atom thus:



The reverse changes occur on acidifying the pseudo-ammonium base, which passes into the true ammonium salt.

The theory has been used to interpret the changes which diazonium salts undergo when acted upon by solutions of alkalis, alkali cyanides, and sulphites (p. 162). Under these circumstances the diazonium salt is converted into the *syn* diazotate, diazocyanide, and diazo-sulphonate.



Density and Volume. Schaum¹ observed that freshly distilled acetoacetic ester acquires a different density after standing, and recognized the fact as evidence of isomeric change. From the density of acetoacetic ester and its solutions in various solvents Traube² calculated the molecular solution volumes, and showed that in the majority of solvents the molecular volume undergoes a gradual change which can only be explained on the assumption of the existence of two esters in equilibrium.

Electrical Oscillations. By the use of a specially contrived apparatus Drude³ examined the absorptive power of organic compounds for electrical oscillation, and found that whilst hydroxyl compounds absorb the oscillations readily, aldehydic and ketonic compounds do not. The method has been applied to the investigation of dynamic isomers, and the results are in substantial agreement with those of Brühl and Perkin.

¹ Ber., 1898, 31, 1964.

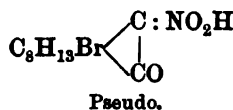
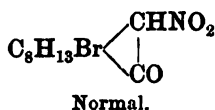
³ Ber., 1897, 30, 940.

² Ber., 1896, 29, 1715.

Acetoacetic ester does not absorb and is ketonic, oxalacetic ester absorbs strongly and is therefore mainly enolic. The change in absorption which accompanies the passage of the liquid to the solid form of formylphenylacetic ester agrees with the observations of Wislicenus. Many other compounds have been studied with similar results.

Optical Activity. The large differences in optical activity of many dynamic isomers have been turned to excellent account as a means of distinguishing the two forms, and of following the equilibrium changes which occur under different conditions. The method has been utilized by Lowry¹ in the study of nitrocamphor and π -bromonitrocamphor, and by Lowry and E. F. Armstrong² in that of the different glucoses and glucosides.

The dynamic isomers of π -bromonitrocamphor and pseudo π -bromonitrocamphor are probably represented by the following formulae:



Both compounds have been isolated by crystallization from different solvents: the one, which from its high rotation is regarded as the pseudo form, melts at 142° and has a specific rotation of $[\alpha]_D = +188^\circ$, and the other melts at 108° and has the value $[\alpha]_D = -51^\circ$. When either substance is dissolved in various media an equilibrium mixture of the two isomers results. A 3.83 per cent. benzene solution at 15° reaches a constant rotation of $[\alpha]_D = -38^\circ$, and consists then of an equilibrium mixture of one part of pseudo and seventeen parts of the normal compound. This change of rotation has been named by Lowry *mutarotation*. Nitrocamphor, though only known in one crystalline modification, *m. p.* 100° , nevertheless when dissolved in various solvents shows the same kind of change as the bromo-derivative, thereby indicating the existence of an equilibrium mixture of the two forms. Simon³ suggested, and Lowry and E. F. Armstrong⁴ have since shown, that the α , β , and γ modifications of glucose, which have the specific rotations

$$[\alpha]_D = +105^\circ, +52.5^\circ, \text{ and } +22^\circ$$

respectively, consist in all probability of two stereoisomeric α - and γ -glucoses having the rotations $[\alpha]_D = +105^\circ$ and $+22^\circ$, which

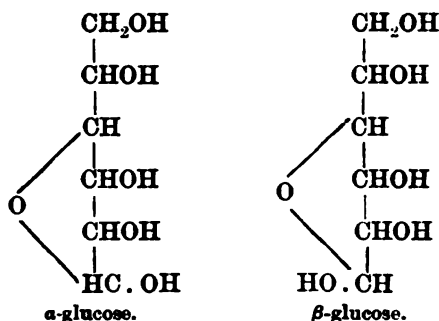
¹ *Trans. Chem. Soc.*, 1899, 75, 235.

² *Compt. rend.*, 1901, 132, 487.

³ *Trans. Chem. Soc.*, 1908, 83, 1814.

⁴ *Trans. Chem. Soc.*, 1908, 83, 1805, 1814.

exhibit mutarotation by forming an equilibrium mixture having the intermediate value (see p. 380).



Solubility and Melting-point. Several cases have been referred to in which dynamic isomers have been isolated and their quantity estimated by differences of solubility. The method is, however, limited in its application, since, if crystallization proceeds slowly, isomeric change may occur, and equilibrium is re-established in the solution as soon as the less soluble isomer begins to separate. The second isomer will consequently not crystallize out. Lowry found that this was the case with nitrocamphor, which could only be obtained in one isomeric form. If the separation takes place quickly, or isomeric change is slow, the two isomers will behave like distinct substances and separate according to their solubilities. It is also clear that if isomeric change occurs during solution, the substance will possess an apparent as well as a real solubility depending on the extent of the conversion. Lowry¹ has applied the principle to diagnosing cases of isomeric change by determining the solubility immediately following solution and after an interval has elapsed. As there is an apparent and a true solubility there will exist an apparent and a true melting-point, depending on isomeric change. These changes can best be followed by means of the freezing-point curves of the mixed isomers, as was done in the case of mixtures of enantiomorphs (p. 86).

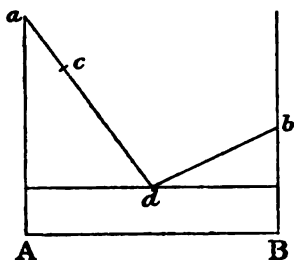


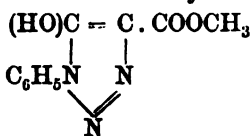
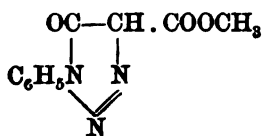
FIG. 31.

In the diagram, ad and bd represent the freezing-point curves of a mixture of two dynamic isomers A , B , and c the freezing-point of the equilibrium mixture after fusion. The true melting-points are

¹ *Trans. Chem. Soc.*, 1904, 85, 1541, 1551.

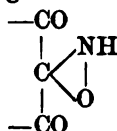
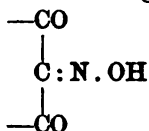
represented by *a* and *b*. If isomeric change occurs on fusion the melting-point of the higher melting isomer *a* will fall, and will become constant when the equilibrium temperature of fusion *c* is reached. Similarly the melting-point of *b* will follow the curve *bdc*, and according to the rate of isomeric change will indicate after fusion a lower or higher melting-point which eventually becomes constant at *c*. If the change is slow the two substances will behave like separate individuals, one of the components first separating, followed by the more fusible eutectic mixture. The temperature above which isomeric change first sets in has been termed by Knorr the *stability limit* of the substance, and if it lies above the melting-point the true melting-point will be given; but the stability limit, though obviously not a fixed point, is usually coincident with the fusion temperature, and in that case the melting-point will not be the true one.¹

Colour. Examples of the differentiation of dynamic isomers by means of colour have already been given. There are many pseudo-acids possessing one colour which, on the addition of a base, are supposed to change into a salt of the normal acid having another colour. Colourless violuric acid, which is the pseudo form, gives pink or violet salts.² Colourless nitrolic acids form red salts. The green solution obtained by adding nitrous acid to phenol probably represents the nitroso compound, whilst the red sodium salt may have the oxime formula. Other examples are the colourless and yellow modifications of acetone dioxalic ester,³ the colourless enol and yellow keto form of Dimroth's⁴ phenyltriazolone carboxylic ester.



Phenyltriazolone carboxylic ester.

The colourless and yellow mesoxamide oxime and its coloured salts⁵ are represented as containing the following isomeric groups:



¹ The behaviour of dynamic isomers on fusion is discussed from the phase rule standpoint by Findlay, *Trans. Chem. Soc.*, 1904, 87, 408.

² Hantzsch, *Ber.*, 1899, 32, 598.

³ Willstätter and Pummerer, *Ber.*, 1904, 37, 3738.

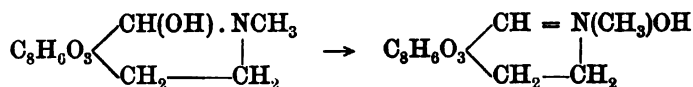
⁴ *Annalen*, 1904, 335, 1.

⁵ Whiteley, *Trans. Chem. Soc.*, 1900, 77, 1040; 1903, 83, 24.

There are also the colourless and yellow silver compounds of the amides,¹ and the colourless nitrophenols and their orange or red salts.²



Absorption Spectra. The ultra-violet absorption spectra have been studied by Hartley, by Dobbie and Lauder, and by Baly and Desch, with results which possess considerable interest. Dobbie, Lauder, and Tinkler³ were able to observe changes in the spectra of solutions of cotarnine and its derivatives which could only be explained by isomeric change.



The observations of Baly and Desch have thrown a new light on the mechanism of isomeric change which will be considered presently.

Theories of Tautomerism. Laar, who was the first to offer a theory of tautomerism, supposed that the mobile hydrogen atom in tautomeric compounds was in a state of constant oscillation, so that both compounds might be regarded as present in the substance in a labile state. This applied to solids as well as to liquids and solutions. The view received support from the observations of von Pechmann, Luxmoore, and others (pp. 182, 184). It has already been stated that phenyltolylbenzamidine forms with ethyl iodide two ethyl derivatives. The result is readily explained on the assumption that the substitution of hydrogen by ethyl occurred at opposite periods of an oscillation. The same view can be applied with equal force to the conversion of benzantialdoxime into a mixture of the oxime and pseudoxime ethers. A similar idea is embodied in Knorr's⁴ theory of the *oscillating double-bond*, in which the rapid shifting to and fro of the double-bond and of the hydrogen atom associated with it, is made accountable for the identity of such substances as the two methyl pyrazoles referred to on p. 186. A very similar explanation is offered by Thorpe⁵ of the identity of the $\alpha\beta$.

¹ Titherley, *Trans. Chem. Soc.*, 1901, 77, 409.

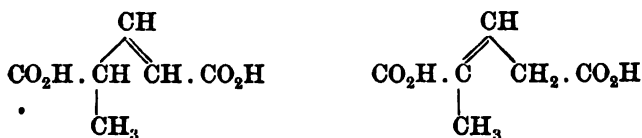
² *Ber.*, 1906, 39, 1084.

³ *Trans. Chem. Soc.*, 1903, 83, 598.

⁴ *Annalen*, 1894, 279, 188.

⁵ *Trans. Chem. Soc.*, 1905, 87, 1680; 1906, 89, 651.

and $\beta\gamma$ -dimethylglutaconic acids and of the α - and γ -methyлаconitic acids.



α - and γ -Methyлаconitic acid.

Allelotropism. Knorr¹ was the first to discuss the subject of tautomerism on a broad, philosophical basis. In a paper on the tautomerism of the dibenzoyl- and diacetyl-succinic esters subsequent to that already referred to (p. 191), he lays down the principle that each substance has its own structure, that when heated above its stability limit it yields an equilibrium or *allelotropic* mixture, and that similar mixtures are formed in solution; the proportion of the isomer depending on the nature of the solvent, the temperature, and the dilution. Finally, he revives Butlerow's view of the nature of the change occurring between the two isodibutylenes to explain isomeric change in general, which he attributes to an intermolecular, and not, as Laar had done, to an intramolecular process. At the same time he recognizes that Laar's oscillation theory may explain very rapid isomeric changes, such as presumably exist in the case of hydrogen cyanide, benzene, the methyl pyrazoles, &c.

Thus Laar's tautomerism or oscillating structures, and Baeyer's pseudomerism or single, stable structures, are limiting cases of allelotropism or equilibrium mixtures of isomers.

Dynamic Isomerism. The theory which has been recently developed by T. M. Lowry² has been moulded on a still broader basis. In place of the word tautomerism and the various other names applied by different observers to indicate different views of the same phenomenon, he has introduced the single expression *dynamic isomerism*, which he defines as *reversible isomeric change*.

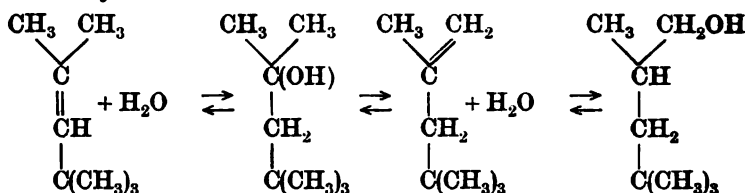
The principle of balanced actions between isomers had already been recognized by Butlerow³ from the results of his inquiry into the action of sulphuric acid on trimethyl carbinol. Butlerow showed that the product consisted of two isomeric isodibutylenes, and he explained their formation on the assumption that equilibrium

¹ *Annalen*, 1899, 306, 332.

² *Trans. Chem. Soc.*, 1899, 75, 211; *Brit. Assoc. Reports*, 1904, p. 193.

³ *Annalen*, 1877, 189, 76.

is established between the isodibutylenes and the corresponding alcohols by means of water.



Butlerow suggested that equilibrium might also exist in the absence of any reagent, and that hydrogen cyanide and cyanate might be equilibrium mixtures of cyanide and nitrile in the one case, and carbimide and cyanogen hydroxide in the other.

Dynamic isomerism includes every form of balanced action between isomers, and therefore embraces not only examples of labile isomeric change, like that of the two formylphenylacetic esters (which are readily interconvertible at ordinary temperatures), but others which are perfectly stable, and only undergo isomeric change on fusion, like ammonium thiocyanate and thiourea.¹



These reactions therefore belong to the type of unimolecular reversible or balanced actions, and may be treated mathematically. According to the theory of reversible reactions a condition of equilibrium is attained when the quantities of the two substances are in a definite ratio, which is determined by the ratio of the velocity constants of the opposing reactions. If k_2 and k_1 are the velocity constants of the two isomeric changes taking place in opposite directions, and x_0 , x_t , and x_∞ the quantities of the original substance at times 0, t , and ∞ , the reaction will proceed according to the equation,

$$\frac{dx}{dt} = k_1(x_0 - x_t) - k_2x_t,$$

which when integrated becomes,

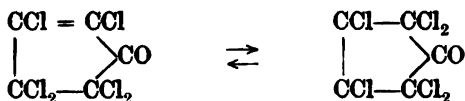
$$k_1 + k_2 = \frac{1}{t} \log \frac{x_0 - x_\infty}{x_t - x_\infty}.$$

If the quantity of one of the substances is known at time t , the value of $k_1 + k_2$, that is, the sum of the velocity constants of the opposing reactions, can be determined and should give a constant. The velocity constant is only subject to variation with change of concentration in case one of the substances acts as a catalyst or

¹ Waddell, *Journ. phys. Chem.*, 1898, 2, 523; Reynolds and Werner, *Trans. Chem. Soc.*, 1908, 83, 1.

undergoes some secondary change. The above equation has been used by Küster,¹ by Lowry,² and others, and the experimental results are in close agreement with the unimolecular law.

Küster applied the equation to the dynamic isomerism of two hexachloroketocyclopentenes.



Hexachloro α -keto β -cyclopentene. Hexachloro α -keto γ -cyclopentene.

The process was conducted by suspending a small quantity of the substance in the vapour of boiling nitrobenzene for a certain length of time and then rapidly cooling. The substances were then converted into the anilides and separated by solvents. When equilibrium was established the mixture consisted of 61.4 per cent. of β - and 38.6 per cent. of γ -compound. Lowry studied the rate of change of solutions of nitro and π -bromonitro camphor by means of the polarimeter.

Every form of isomeric change may be studied from this standpoint, including such processes as optical and geometrical inversion (pp. 80, 117). The racemisation of tartaric acid and the transformation of the two tolane dibromides belong to the same order of phenomenon and are subject to the same law.

The existence of only one representative of two possible isomers like isatin or acetoacetic ester may be regarded as merely a limiting case in which the isomeric form is too labile to exist under the experimental conditions. The same may be said of those reactions which are apparently non-reversible, for the balance may then be assumed to shift so much to one side that little or none of the original substance can be detected. These one-sided or completed reversible reactions will be considered separately.

The Mechanism of Isomeric Change. It will be interesting to attempt to form some idea of the process by which isomeric change is brought about. Laar regarded the change as intramolecular, that is, as a change produced by a direct transference of the atoms in the molecule. Lowry, on the other hand, considers that it is effected by the aid of a third substance which plays the rôle of a catalyst, just as the union of certain gases requires the presence of water.

In support of this view he points to the fact that nitrocamphor³

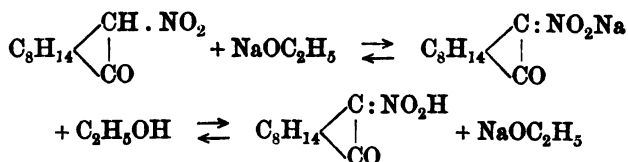
¹ *Zeit. phys. Chem.*, 1895, 18, 171.

² *Trans. Chem. Soc.*, 1899, 75, 224.

³ Lowry, *Trans. Chem. Soc.*, 1899, 75, 219.

and the enolic form of α -benzoyl camphor¹ in chloroform solution will remain unchanged for a long period, but that the dust of the laboratory or the soft glass of the polarimeter tube is sufficient to start the transformation.

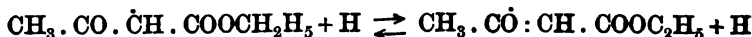
As we have seen, the change from ketonic to enolic form is accelerated by bases, whilst the reverse process is produced by certain solvents. Lowry explains the action of sodium ethoxide on nitrocamphor by supposing that the enolic sodium compound is formed and decomposed reversibly into keto or enol forms until equilibrium is established thus :



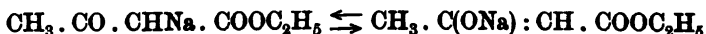
Brühl has suggested that the solvents in question have an ionizing action on the dissolved substance, and the enolic form, being a weak acid and electrolyte, breaks up into a hydrogen ion and an organic ion, and the latter has a tendency to recombine with the hydrogen ion to form the non-ionized ketonic compound.

The objection to this view is that it implies a complete conversion of the enolic to the ketonic type, which is not always the case. Lapworth² has suggested that the change takes place in the negative organic ion through an alteration in the position of the free bond or affinity. In the case of bases the acceleration is due to the diminution of hydrogen ions by increasing the concentration of hydroxyl ions and at the same time increasing that of the organic ions.

The interconversion of the ketonic and enolic form of acetoacetic ester will be represented as follows :



so that in a sodium ethoxide solution both ketonic and enolic forms will be present in equilibrium, a condition which is virtually equivalent to the presence of the two sodium compounds :



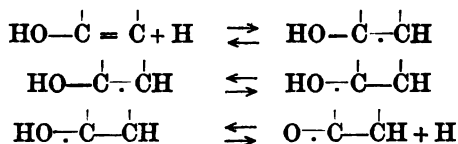
It should be noted that the structure of the sodium compound which separates from solution will depend on the relative solubilities of two isomeric forms, and, if equilibrium is rapidly established, will

¹ Forster, *Trans. Chem. Soc.*, 1901, 79, 997.

² *Trans. Chem. Soc.*, 1902, 81, 1508.

be independent of the composition of the equilibrium mixture in solution.

It frequently happens that acids have an opposite effect to bases and retard or suspend isomeric change, in other cases they act as catalysts and accelerate it.¹ When the latter occurs another explanation than that of the diminution of hydrogen ions must be found, and Lapworth has suggested that they may cause the change by forming a complex ion with the organic compound, which functions as a weak base like ammonia, and then undergoes internal rearrangement as follows, the dot indicating the temporary disposition of the free affinity:



Baly and Desch² have been led from their observations on the ultra-violet absorption spectra of various dynamic isomers to a very different view of the mechanism of the process. They point out from their own and Hartley's observations that no banded absorption is produced either by a hydroxyl group or double bond, yet they obtained banded spectra with acetylacetone and acetoacetic ester and its metallic compounds, and with other substances exhibiting dynamic isomerism; but not with pure enolic or ketonic substances. They conclude, therefore, that there is a vibration within the molecule of these substances which is synchronous with the frequency of the light-waves absorbed. This vibration cannot be attributed to the oscillation of the hydrogen atom or metal within the molecule, because the observed oscillation frequencies are the same for both, and it is not probable that the different kinds of atoms would oscillate with equal rapidity or with that of rays of ultra-violet light. The process is therefore ascribed to a vibration set up by an alteration in the linking which accompanies isomeric change of the keto-enol type.

COMPLETED ISOMERIC CHANGE

Although it is generally recognized that the isomeric changes which appear to take place in only one direction may be merely limiting cases of reversible reactions in which the original substance virtually disappears, it is convenient, until these reactions have been

¹ Lapworth, *Trans. Chem. Soc.*, 1902, 81, 1508; 1908, 83, 1123; 1904, 85, 30.

² *Trans. Chem. Soc.*, 1904, 85, 1029; 1905, 87, 766, 1882.

more fully studied, to place them in a separate group by themselves.

An isomeric change which is completed in one direction is a unimolecular reaction, and, provided there are no disturbing by-reactions, represents the simplest type of chemical change. It follows a logarithmic law, and may be studied as a problem in chemical dynamics. According to the mass law the rate of change will be proportional to the quantity of substance present at any given time, or conversely, if the change follows the mass law and the quantity of substance present at any time is ascertained, the velocity constant k can be calculated from the well-known equation,

$$k = \frac{1}{t} \log \frac{a}{a-x},$$

in which t is the time, a the amount of substance at the beginning of the observation, and x the amount transformed after an interval of time t .

The velocity constant can of course only be determined where the change takes place sufficiently slowly for the composition of the mixture undergoing transformation to be ascertained, and where either the process can be suddenly arrested or the products quickly analysed. It is clear that these conditions render the study of many isomeric changes difficult or impossible, and the result has been that only a very few have been examined dynamically. In such cases as the transformation of acetochloranilide into *p*-chloracetanilide¹ (p. 217), that of diazoaminobenzene into aminoazobenzene² (p. 221), of acetophenoneoxime into acetanilide³ (p. 213), it has been found that the reaction follows the mass law.

Generally speaking, these completed isomeric changes result not in the transference of a single mobile hydrogen atom, but in the interchange of groups, reactions which are usually, though not invariably, induced by the presence of strong acids. It would appear, therefore, that on the ionic theory the change is produced by the catalytic action of hydrogen ions. This view has been advanced by Goldschmidt and Reinders in the case of diazoaminobenzene, by observing that the velocity of isomeric change from diazoaminobenzene to aminoazobenzene increases with the proportion of catalyst (an aniline salt) and with the dissociation constant of the acid of the salt.⁴ A similar view has been expressed by Beckmann in reference to the reaction which bears his name.⁵

¹ J. J. Blanksma, *Rec. trav. Pays Bas*, 1902, 21, 366; 1903, 22, 290.

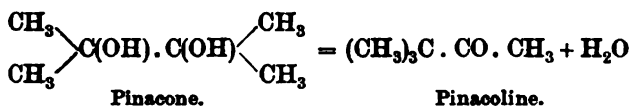
² Goldschmidt and Reinders, *Ber.*, 1896, 29, 1869, 1899.

³ Lobry de Bruyn and Sluiter, *Koninklijke Akad. van Wetenschappen*, 1904, 773.

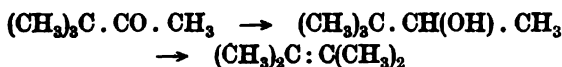
⁴ *Ber.*, 1896, 29, 1905.

⁵ *Ber.*, 1894, 27, 300.

Transference of Hydrocarbon Radicals (from Carbon to Carbon). The pinacone-pinacoline conversion is an example of the transposition of a radical from carbon to carbon ; strictly speaking, it is not an isomeric change, for the process is accompanied by the loss of water ; but the reaction may be conveniently discussed here. Fittig¹ found that when tetramethyl pinacone is distilled with dilute sulphuric acid it is converted into pinacoline, or tertiary butyl methyl ketone.

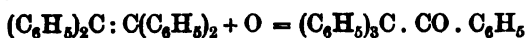


On reduction with hydriodic acid, pinacoline loses oxygen and yields tetramethylethylene, in which a methyl group wanders back to the original carbon.

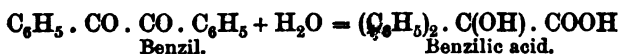
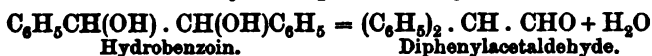


Precisely similar results have been obtained with benzpinacone.

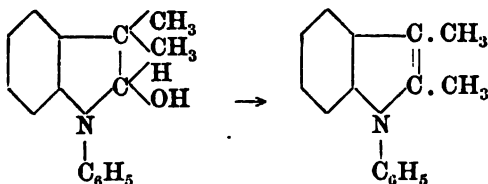
Another curious change is that produced by oxidation which transforms tetraphenylethylene into benzoyltriphenylmethane.²



To the same class of reactions belong the conversion of hydrobenzoin into diphenylacetaldehyde under the action of sulphuric acid and of benzil into benzilic acid by fused potassium hydroxide.



The same kind of change has been shown by Brumer,³ Wolff,⁴ and Knorr⁵ to occur in ring compounds. To take one example, Brumer found that phenyldimethyl indolinol is converted by hydrogen chloride into a dimethyl indole with the loss of a molecule of water.



¹ *Annalen*, 1860, 114, 56.

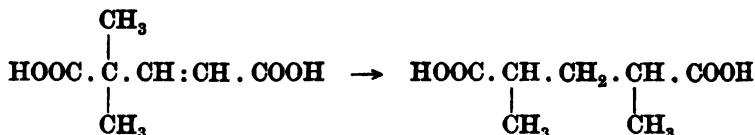
² Delacré, *Compt. rend.*, 1896, 123, 1202 ; 1896, 123, 245.

³ *Monatsh.*, 1896, 17, 276 ; 1900, 21, 156.

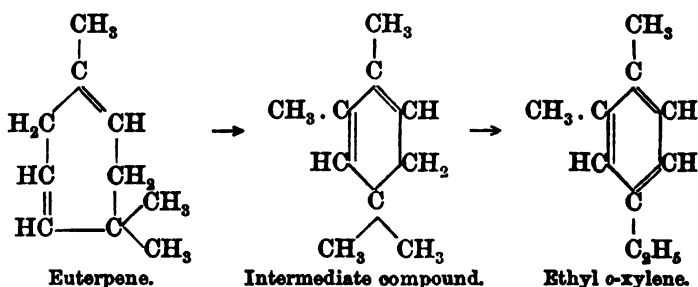
⁴ *Annalen*, 1902, 322, 351.

⁵ *Ber.*, 1903, 36, 1272.

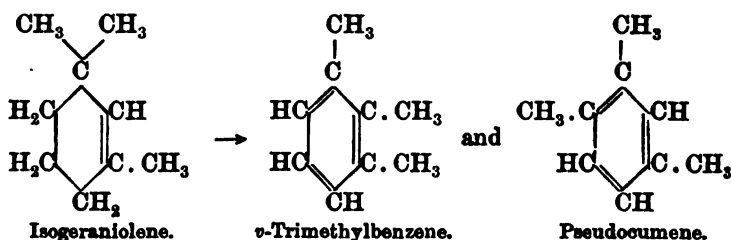
The mechanism of this change is still obscure.¹ The wandering of a methyl group from one carbon atom to another is occasionally met with among other groups of compounds. Blaise² found that *α*-dimethylglutaconic acid on reduction with hydrogen iodide gives *αα*-dimethylgluconic acid,



and among aromatic compounds a similar process has also been observed. Baeyer³ has shown that by exhaustive bromination of euterpene, isogeraniolene, and similar compounds, the methyl group changes its position in the ring. Euterpene gives ethyl *o*-xylene probably in the following steps:



whilst isogeraniolene gives bromine derivatives of two trimethyl benzenes.



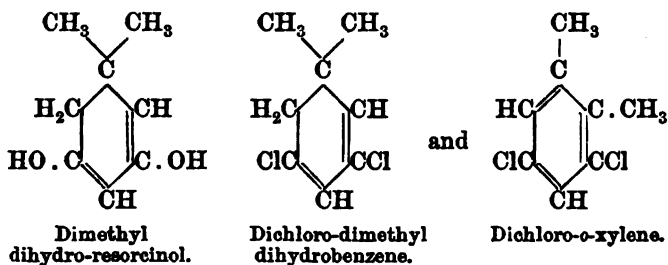
Also Crossley and Le Sueur⁴ have found that dimethyl dihydroresorcinol yields with phosphorus pentachloride a small quantity of an *o*-xylene derivative.

¹ See Werner and Grob, *Ber.*, 1904, 37, 2887.

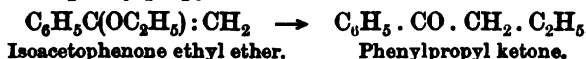
² *Compt. rend.*, 1908, 136, 881.

³ *Ber.*, 1896, 31, 2067; 1899, 32, 2430.

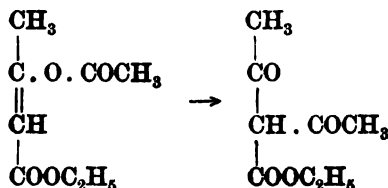
⁴ *Trans. Chem. Soc.*, 1902, 81, 827.



Transference of Radicals (from Oxygen to Carbon). Claisen¹ found that isoacetophenone ethyl ether when boiled under pressure changes into phenylpropyl ketone.



He also showed that the acetyl derivative of hydroxycrotonic ester (from acetoacetic ester, acetyl chloride, and pyridine) was transformed by means of potassium carbonate and a little acetoacetic ester, or by sodium acetoacetic ester into diacetoacetic ester.²



The corresponding alkyl derivatives do not undergo this conversion. Acetophenone O-benzoate,³ on the other hand, is converted in much the same way by the action of metallic sodium and a little acetophenone into the sodium compound of dibenzoylmethane.



These reactions are attributed by Claisen to the displacement by the alkali metal of the acid radical, which is thereby thrust on to the adjoining carbon atom. He perceives in the above isomeric change the cause of the formation of diacetoacetic ester when acetyl chloride acts upon sodium acetoacetic ester. The unstable O-acetyl derivative which is first formed passes into the stable C-acetyl compound (p. 175). The theory fails, however, to explain the non-appearance of the very stable O-alkyl derivatives when the alkyl iodides react with the sodium compound.⁴

A reaction of a character similar to the foregoing is Kolbe's well-

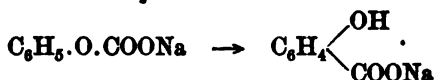
¹ Ber., 1896, 29, 2931.

² Ber., 1900, 33, 3778.

³ Claisen and Haase, Ber., 1903, 36, 3678.

⁴ See also Dieckmann and Stein, Ber., 1904, 37, 3392.

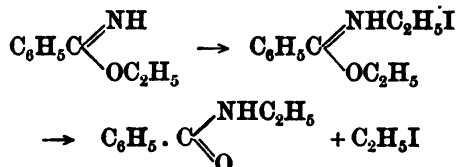
known salicylic acid process in which phenyl sodium carbonate is converted into sodium salicylate.



From Nitrogen to Carbon. The interchange of radicals between nitrogen and carbon is presented by the conversion of alkyl isocyanides into cyanides at a high temperature.¹



From Oxygen to Nitrogen. Examples of the transference of an alkyl group from oxygen to nitrogen are very numerous. Hofmann and Olshausen² and also Pomarew³ found that normal cyanuric esters pass into the isocyanuric esters on heating, and Wheeler and Johnson⁴ showed that imino ethers are converted into alkyl amides on heating with alkyl iodides. Benzimino ethyl ether heated to 100° with ethyl iodide yields ethyl benzamide. That the reaction may be brought about by addition of alkyl iodide seems not improbable from an observation of Wislicenus and Körber.⁵



Wislicenus and Goldschmidt⁶ noticed that in many cases (benzimino ethyl ether is an exception) mere heating will convert the imino ether into the amide. The imino ether of formanilide slowly changes at 200° into ethylformanilide,



and methoxycaffeine gives tetramethyluric acid. Lander,⁷ who has repeated the experiments, finds this isomeric change, by heat alone, not easy to effect in any case, and does not regard it as a simple transformation (p. 181).

Similar changes have been observed by Auwers⁸ in which acyl and alkyl radicals of aminophenol derivatives pass from oxygen to nitrogen,

¹ Wade, *Trans. Chem. Soc.*, 1902, 81, 608.

² *Ber.*, 1870, 3, 272.

³ *Amer. Chem. Journ.*, 1899, 21, 187.

⁴ *Ber.*, 1900, 33, 1467.

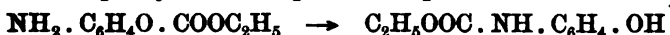
⁵ *Annalen*, 1904, 332, 159.

⁶ *Ber.*, 1885, 18, 3269.

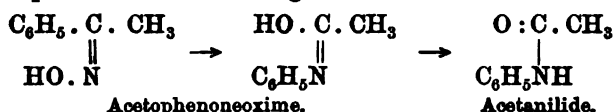
⁷ *Ber.*, 1902, 35, 164.

⁸ *Trans. Chem. Soc.*, 1903, 83, 411.

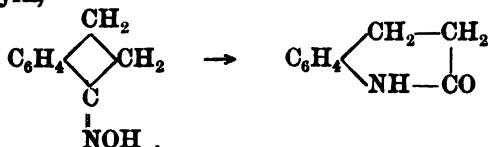
and Stieglitz and Upson¹ have studied an analogous process in which aminophenylcarbonate passes into phenolurethane.



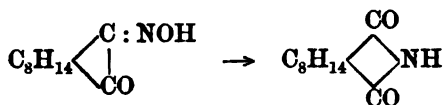
Beckmann Change (from Carbon to Nitrogen). The reaction has already been described and consists of an interchange of organic radical and hydroxyl in the oximes (p. 149). A simple illustration is the conversion of acetophenoneoxime into acetanilide, which is usually explained in the following fashion:



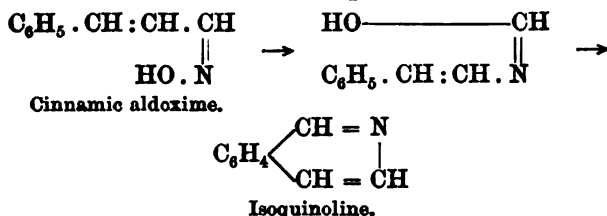
The change can be effected by numerous reagents, such as the chlorides of phosphorus and other organic and inorganic acid chlorides, sulphuric and hydrochloric acid, acetic acid, and anhydride and phosphorus pentoxide. The reaction can be applied not only to the oximes of open chain aliphatic and aromatic ketones, but to those of cyclic structures like α -hydrindone-oxime which changes into hydrocarbostyryl,²



and isonitrosocamphor which passes into camphorimide.³



Another curious manifestation of the Beckmann change is the conversion of cinnamic aldoxime into isoquinoline.⁴



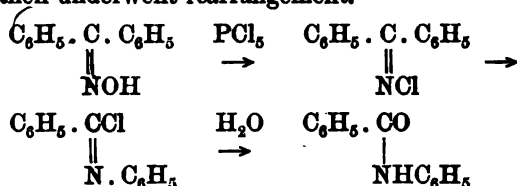
¹ *Amer. Chem. Journ.*, 1904, 31, 458; 1904, 32, 18.

² Kipping, *Proc. Chem. Soc.*, 1898, 9, 240.

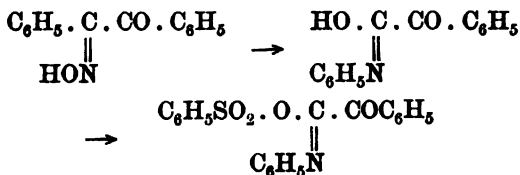
³ Angeli, *Real. Accad. dei Lincei* (5), 1, 441.

⁴ Bamberger, Goldschmidt, *Ber.*, 1894, 27, 1955.

The mechanism of the change in spite of careful study is still very obscure. The original reagent, phosphorus pentachloride, used by Beckmann, and the formation of benzanilide iminochloride from benzophenoneoxime, which was isolated in the course of the decomposition, rendered it probable that the hydroxyl was replaced by chlorine and then underwent rearrangement.

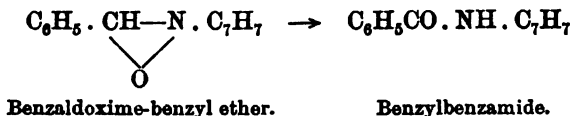


But the action of other reagents like sulphuric acid cannot be explained in precisely the same way. The radical of the acid might, however, enter in place of hydrogen or hydroxyl and render the latter labile and more prone to rearrangement. The behaviour of γ -benzilmonoxime towards benzenesulphonic chloride, with which it combines in pyridine solution, renders some such explanation probable. It is represented by Werner and Piguet¹ in the following way :



If this is a correct interpretation it indicates that the process is not dependent in the first instance on the hydroxyl being replaced by a negative group, although there is nothing to show that the interchange precedes rather than follows combination with the sulphonic chloride.

The small quantity of phosphorus pentachloride or oxychloride necessary to convert benzo- and aceto-phenoneoxime into the corresponding anilide, and the trace of acid chloride required to transform benzaldoxime benzyl ether into benzylbenzamide,



led Beckmann² to formulate the somewhat vague hypothesis that the process consists in the transposition of electrically charged radicals

¹ Ber., 1904, 37, 4295.

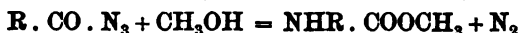
² Ber., 1894, 27, 300.

or ions, and that the reagent merely acts as a catalyst by increasing the velocity of the interchange.

Stieglitz¹ takes a very different view of the mechanism of the process. He groups together under one head the Hofmann method for converting amides into amines,



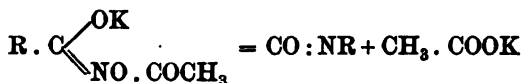
Curtius' process for producing urethanes from azides,



including the formation of methylene phenylimine from benzyl azide,

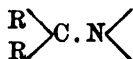


the conversion of acyl hydroxamic salts into carbimides,²



and the Beckmann change. In all of these reactions the radical passes from carbon to nitrogen, and a general explanation has been furnished to include them all.

Stieglitz shows that the various changes described above are completely arrested if a radical is attached to the nitrogen atom, as for example in acetylchlorimino-amyl ether $\text{CH}_3 \cdot \text{CO} \cdot \text{NCl}(\text{C}_5\text{H}_{11})$ and in the chlorimino ethers of the formula $\text{RC}(\text{:NCl})\text{OR}^1$. This is scarcely surprising in view of the stability of the imino ethers (p. 212). Nevertheless, he infers that before the change can occur a univalent nitrogen atom must be present. The bromamide, azide, and acyl hydroxamic salts yield $R \cdot \text{CO} \cdot \text{N} <$ and the oximes yield



In the present incomplete state of the investigation it is scarcely profitable to pursue the argument further; but it may be pointed out that an explanation which includes only a few arbitrarily selected cases out of a large number of isomeric changes is not likely to lead to a satisfactory generalization.

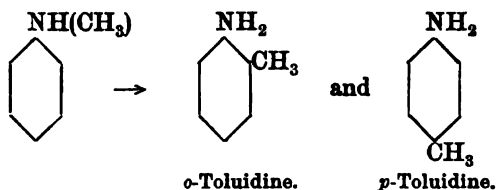
Transference of Radicals from Side-Chain to Nucleus (from Nitrogen to Nuclear Carbon). This is a type of conversion which is most commonly experienced. It includes the reaction of Hofmann and Martius,³ which consists in heating the hydrochloride of aromatic

¹ *Amer. Chem. Journ.*, 1896, 18, 751; 1908, 29, 49, 289; 1908, 30, 899, 412.

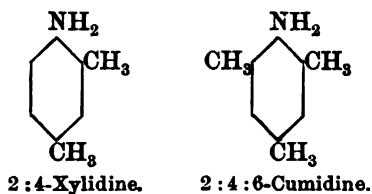
² Hantzsch, *Ber.*, 1894, 27, 1256.

³ *Ber.*, 1871, 4, 742; 1872, 5, 704; 1874, 7, 526.

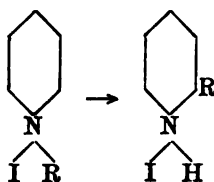
methylamino compounds to 250–350° when the methyl group is transferred from the nitrogen to the *o*- and *p*-carbon of the nucleus and the nuclear hydrogen to the nitrogen.



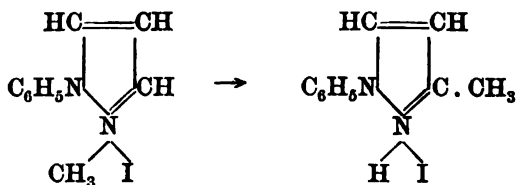
The process may be repeated until a second or third methyl group is introduced, when it comes to an end.



An analogous reaction is the formation of α -alkyl pyridines from the alkyl pyridinium iodides (p. 537),



and phenylmethyl pyrazole from phenylpyrazole methyl iodide.¹

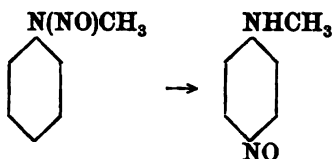


Fischer and Hepp² found that the nitrosamine of monomethyl-

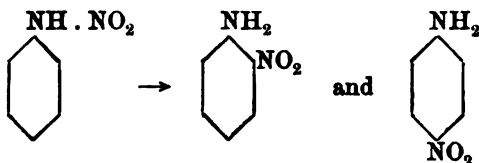
¹ Balbiano and Maschetti, *Real. Accad. Lincei*, 2, (1), 114.

² *Ber.*, 1886, 19, 2991.

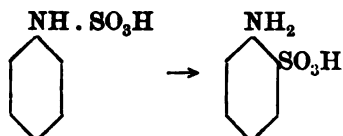
aniline when treated with hydrogen chloride in alcohol solution passes into *p*-nitroso-methylaniline.



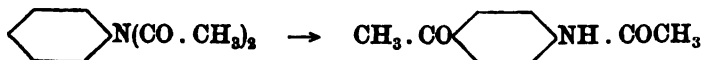
Bamberger¹ discovered that phenylnitramine undergoes a similar change to *o*- and *p*-nitraniline in presence of mineral acids even in the cold.



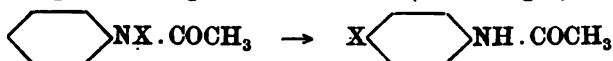
Phenylsulphamic acid, $\text{C}_6\text{H}_5\text{NH}\cdot\text{SO}_3\text{H}$, which Bamberger and Hindermann² obtained by the action of sulphur dioxide on phenylhydroxylamine, changes in the cold into aniline *o*-sulphonic acid on the addition of acetic acid and a few drops of sulphuric acid.



Bamberger and Kunz³ further observed that on heating the ortho-compound to 180–190° with strong sulphuric acid the latter was converted into the para-compound (sulphanilic acid). The above changes may indicate the course of the reaction between sulphuric acid and aniline at a high temperature, which is the common method for preparing the sulphanilic acid. Similar to the changes studied by Bamberger are the conversion of diacylanilides into acylamino ketones⁴ by means of zinc chloride,



and the transformation which acylchloro- and bromo-anilides, &c., undergo in presence of glacial acetic acid⁵ (X = halogen).



¹ Ber., 1898, 26, 471, 482; 1894, 27, 359; 1897, 30, 1248.

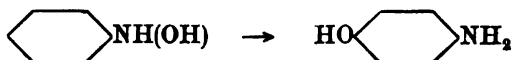
² Ber., 1897, 30, 654.

³ Ber., 1897, 30, 2276.

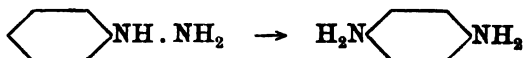
⁴ Chattaway and Lewis, Trans. Chem. Soc., 1904, 85, 886, 589.

⁵ Chattaway and Orton, Trans. Chem. Soc., 1899, 75, 1046.

The formation of *p*-aminophenols from phenylhydroxylamine and its derivatives by the action of mineral acids¹

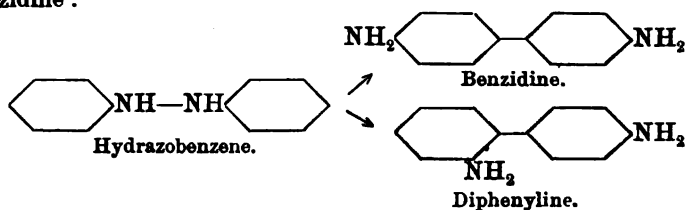


and of *p*-phenylenediamine from phenylhydrazine² by heating with strong hydrochloric acid to 200°



are examples of the same general process.

Benzidine Conversion. The well-known change of hydrazobenzene to benzidine on boiling with mineral acids, known as the benzidine conversion, is analogous in many respects to the foregoing reactions. Zinin³ found that when azobenzene is reduced and boiled with sulphuric acid, benzidine or *p*-diamino-diphenyl is formed. Hofmann⁴ subsequently showed that an intermediate product, hydrazobenzene, is produced during reduction, and that this is the substance which undergoes the transformation. Schultz⁵ then took up the investigation and discovered a small quantity of a second isomer, called diphenylene, which is produced simultaneously with benzidine :



From the formulae it will be seen that the attachment between two nitrogen atoms in hydrazobenzene is substituted by that of two carbon atoms of the nuclei, the amino groups being transferred to the two para positions in benzidine or to one para and one ortho in diphenylene. A simple way of visualizing the change is to suppose the two nuclei in hydrazobenzene to separate, and in the one case to make half a complete revolution before joining up again, and in the other case for one nucleus to be turned through 180° and the other through 60° before joining.

¹ Bamberger, *Ber.*, 1894, 27, 1349.

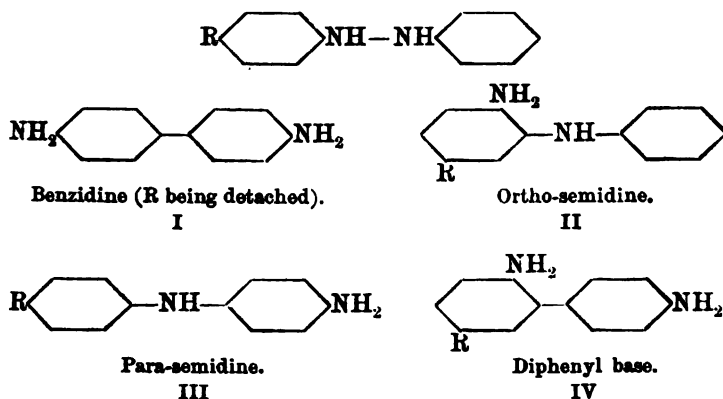
² Thiele and Wheeler, *Ber.*, 1895, 28, 1538.

³ *J. prakt. Chem.*, 1845, 36, 93.

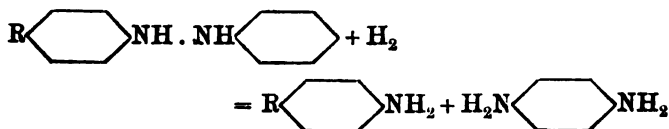
⁵ *Annalen*, 1881, 207, 811.

⁴ *Jahresb.*, 1868, 424.

In a series of papers published by Jacobson and his pupils¹ the results of subjecting substituted hydrazobenzenes to the action of hydrochloric acid have been studied. If, for example, the para position to the nitrogen in hydrazobenzene is occupied in one or both nuclei, will the conversion into benzidine be prevented, or, if not, what will happen? The method employed by Jacobson was to reduce the azo-derivatives, which are readily obtained, with an alcoholic solution of stannous chloride and hydrochloric acid. The hydrazobenzene compound would thus be formed and simultaneously converted into the required products, which could then be separated, identified, and estimated. The following changes are possible, supposing one nucleus to be substituted in the para position by R:



V. Decomposition of the compound into two molecules of base thus:



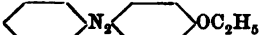
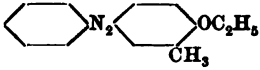
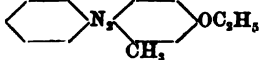
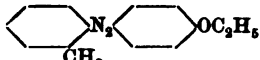
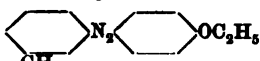
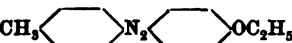
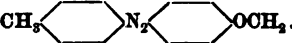
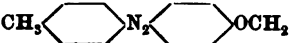
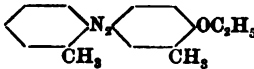
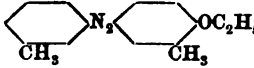
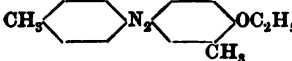
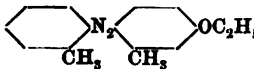
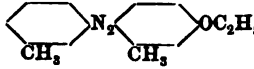
It has been shown that all these reactions may and occasionally do occur, but usually the principal changes are limited to one, or at most two, of the above, the others being subordinate.

The following table contains a summary of the results. In the first column are the elements or groups occupying the position R, and the signs 0, I, II, and III indicate roughly the extent of the changes denoted at the head of the column.

¹ *Annalen*, 1896, 287, 97; 1899, 303, 290.

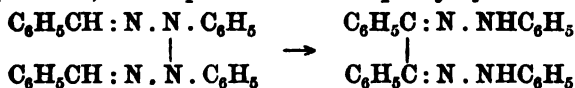
R	Benzidine conversion. R displaced.	Ortho- semidine.	Para- semidine.	Diphenyl base.
Cl				
Br				
I	?		0	
OC ₂ H ₅	0			0
OCOCH ₃		0	0	
N(CH ₃) ₂	0		0	
NH.COOCH ₃	0	0		0
CH ₃	0		?	?
COOH		?	0	0

The following table contains the percentage amount of product representative of each change where one or both para positions are occupied:

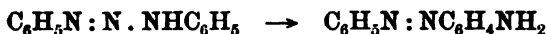
Azo-compound.	Ortho- semidine.	Para- semidine.	Decom- position.
	42	14	36
	50	21	20
	—	47	41
	—	51	36
	28	26	34
	18	—	72
	—	—	77
	—	—	78
	29	36	33
	48	10	18
	50	—	21
	—	58	48
	—	50	44

The main points of interest to be derived from the above table are, firstly, that substitution of both *p*-positions determines decomposition into two molecules of base, and, secondly, that the presence of methyl groups in the ortho position to the azo group, irrespective of the nucleus, diminishes the ortho-semidine conversion. The latter observation appears to be intimately connected with those anomalous reactions which are discussed under *steric hindrance* (p. 224).

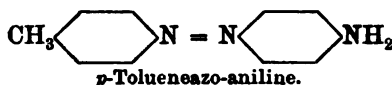
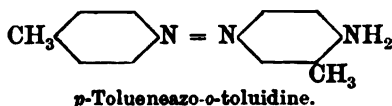
A change closely analogous to the benzidine conversion has been observed by Ingle and Mann¹ in the action of alkalis on dibenzal-phenylhydrazone, which passes into benzilphenylhydrazone.



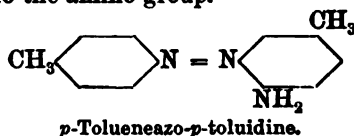
Diazoamino-Aminoazo Conversion. The conversion of diazoamino compounds into aminoazo derivatives by the action of a small quantity of hydrochloride of the aromatic base was discovered by Kekulé in 1866.



Nietzki² found that a similar reaction failed with *p*-diazoamino-toluene and *p*-toluidine hydrochloride, but was successful if the toluidine salt were replaced by the hydrochloride of *o*-toluidine or aniline, giving rise to the following two products:



The failure of *p*-toluidine to combine was due to the fact that the azo nitrogen attaches itself by preference to the carbon para to the amino group, and in *p*-toluidine it is already appropriated. Nevertheless, the reaction with *p*-toluidine was subsequently found by Zincke and Jaenke³ to yield a certain quantity of *p*-tolueneazo-*p*-toluidine, in which the azo nitrogen attaches itself to the carbon in the ortho position to the amino group.

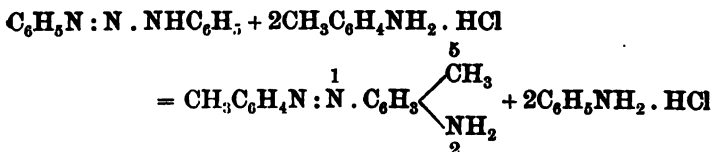


¹ *Trans. Chem. Soc.*, 1895, 67, 606.

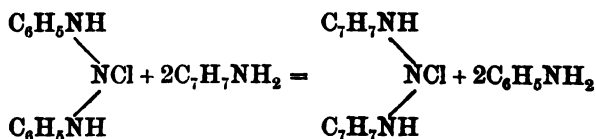
² *Ber.*, 1877, 10, 666.

³ *Ber.*, 1888, 21, 548.

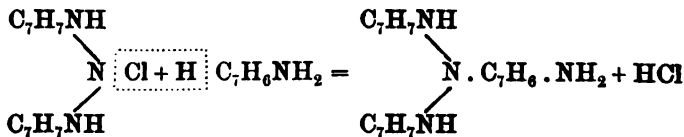
The same observers, in the course of the same investigation, made it quite clear that the conversion is the result not of an intramolecular, but of an intermolecular process, for they obtained aminoazo-*p*-toluene from diazoaminobenzene, and *p*-toluidine hydrochloride dissolved in *p*-toluidine.



A much more complete study of the change has been carried out by Goldschmidt and his collaborators.¹ They have followed the course of the reaction, where interchange of radicals was effected, by determining the alteration of freezing-point and the nature of the products formed during the conversion. In this way they found that the interchange of radicals occurs in the diazonium stage, that is, before the aminoazo conversion sets in. They interpret the results as follows: the production of aminoazotoluene from diazoaminobenzene and *p*-toluidine hydrochloride dissolved in *p*-toluidine consists in the formation of an additive compound of hydrogen chloride with diazoaminobenzene, which is very unstable, and in which aniline residues are replaced by toluidine residues.



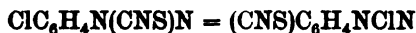
The product in presence of a large excess of toluidine then unites with another molecule of *p*-toluidine,



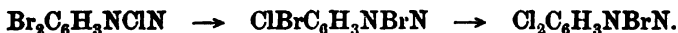
which breaks up into toluidine and aminoazotoluene. In subsequent papers, already referred to (p. 208), the velocity of the change diazo-amino-aminoazo has been studied and shown to follow the mass law for unimolecular reactions.

¹ Ber., 1892, 25, 1347; 1896, 29, 1369, 1899.

Interchange of Acid Radicals (from Nitrogen to Nuclear Carbon). Hantzsch¹ has observed an interchange of halogen of the nucleus with the acid radical of a diazonium salt in the case of diazonium halides and thiocyanates. Thus chlorobenzenediazonium thiocyanate, when dissolved in alcohol containing hydrogen chloride, passes into thiocyanobenzenediazonium chloride,



and this change is facilitated by increasing the number of halogen atoms in the nucleus. An interchange of chlorine and bromine has also been noticed under similar circumstances; di- and tri-bromobenzenediazonium chloride exchange bromine for chlorine. Dibromobenzenediazonium chloride may be converted step by step into dichlorobenzenediazonium bromide.



Mechanism of Isomeric Change. At present there is no theory which covers every form of isomeric change. Although some chemists consider that all these processes are intermolecular and not intramolecular, and due to the intervention of a third substance or catalyst, there is no evidence that this is always the case, and the subject must await the results of future research.

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Brit. Assoc. Reports, 1904, p. 198, by T. M. Lowry.

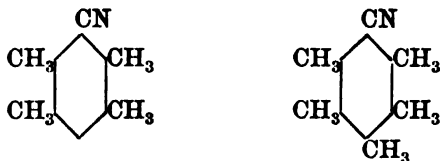
¹ *Ber.*, 1896, 29, 947; 1897, 30, 2334.

CHAPTER VI

STERIC HINDRANCE

From time to time curious irregularities have been observed in the progress of certain typical reactions. These isolated and scattered examples have now been correlated and traced to one fundamental cause, that of *steric hindrance*. The term is intended to denote the influence exerted on a reacting group by the spatial disposition of neighbouring atoms.

As far back as 1872 Hofmann found that dimethylxylidine $(\text{CH}_3)_2\text{C}_6\text{H}_3\text{N}(\text{CH}_3)_2$, dimethylmesidine $(\text{CH}_3)_3\text{C}_6\text{H}_2\text{N}(\text{CH}_3)_2$, and pentamethylaminobenzene $(\text{CH}_3)_5\text{C}_6\text{H}.\text{NH}_2$ give little or no quaternary ammonium compounds when heated with methyl iodide to 150° , and concluded that 'this inability to unite with methyl iodide must depend upon some kind of molecular arrangement'.¹ In 1888 Merz and Weith² found that perchloro- and perbromo-benzonitrile and hexachloro- α -naphthonitrile cannot be hydrolysed by the usual reagents, and in the following year Hofmann made the same observation in regard to tetramethyl- and pentamethyl-benzonitrile.



During the years 1891 and 1892, in a more extended investigation, Claus and his pupils showed that resistance to hydrolysis is greatly enhanced if one, and still more, if both ortho positions to the cyanogen group are substituted by halogen alkyl or nitro groups.³

In 1889 Jacobson⁴ noticed that pentamethylbenzamide



(obtained by the action of aluminium chloride on a mixture of chloroformamide and pentamethylbenzene) completely resists

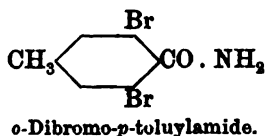
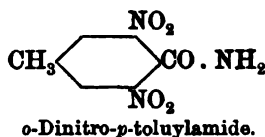
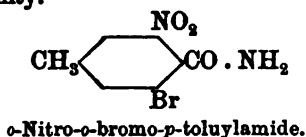
¹ Ber., 1872, 5, 713, 718; 1875, 8, 61.

² Ber., 1888, 16, 2886, 2892.

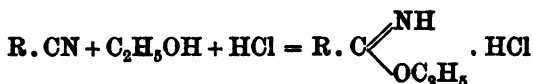
³ Annalen, 1891, 265, 378; 266, 225; 1892, 269, 212 et seq.

⁴ Ber., 1889, 22, 1219.

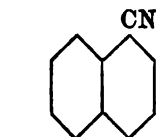
hydrolysis, and Claus¹ again pointed out that, like the nitriles, many diortho-substituted derivatives of *p*-toluylamide exhibit unusual stability.



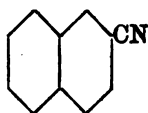
Since then the conditions which determine the hydrolysis of cyanides and amides have been made the subject of more careful study by Sudborough and by Remsen and Reid, and will be referred to again (p. 236). In 1890 Pinner² observed similar anomalies in the preparation of imino-ethers from nitriles by the action of alcohol and hydrochloric acid, which usually takes place according to the equation:



Certain ortho-substituted nitriles refused to react. Neither *o*-tolu-nitrile, 2,4 dimethylbenzonitrile, nor α -naphthoic nitrile (which may be regarded as an ortho-substituted compound) give imino ethers, whereas β -naphthoic nitrile enters readily into the reaction.

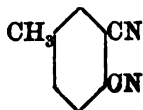


α -Naphthoic nitrile.



β -Naphthoic nitrile.

And, again, both cyanogen groups in isophthalic and terephthalic nitrile readily react, whereas in homophthalic nitrile only one cyanogen group forms an imino ether.

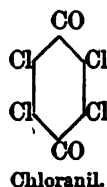
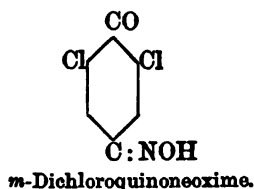
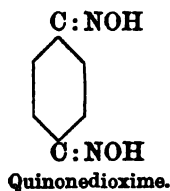


Homophthalic nitrile.

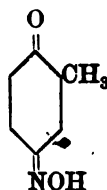
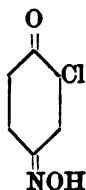
¹ *Annalen*, 1891, 265, 364; 266, 223; 1892, 269, 203.

² *Ber.*, 1890, 23, 2917.

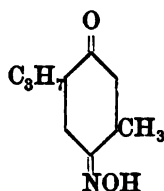
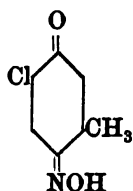
Another series of observations belonging to the same class of phenomena was the subject of a careful study by Kehrman¹, who found that ortho substitution in the quinones retards or inhibits the formation of oximes. Quinone gives a dioxime, *m*-dichloroquinone yields a monoxime, and chloranil gives none.



In the case of mono-substituted quinones, such as monochloroquinone and toluquinone, the oxygen which has no ortho substituent is first replaced by the oxime group before the second oxygen reacts.



In the case of para-disubstituted quinones containing a halogen and a methyl group, the oxime group replaces oxygen in the ortho position to the alkyl group. Where two alkyls are present oxygen is first replaced in the ortho position to the smaller group. Examples of this are afforded by *p*-chlorotoluquinone and thymoquinone.

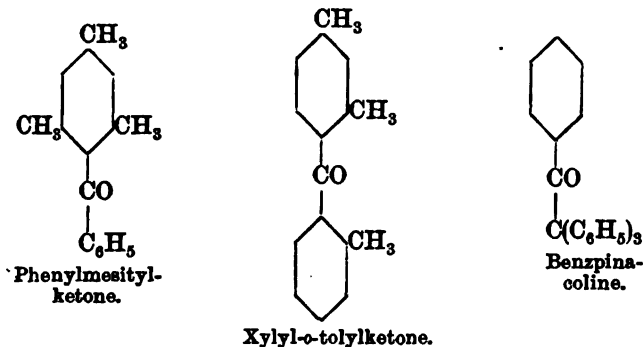


Kehrman concluded that it is less the nature of the substituents (halogen or alkyl) than their presence in the ortho position to the quinone oxygen which interferes with the reaction.

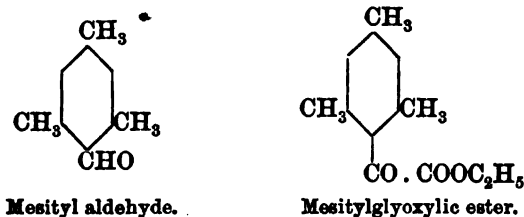
Similar irregularities have frequently been observed in the forma-

¹ *Ber.*, 1888, 21, 3815; 1890, 23, 3557; *J. prakt. Chem.*, 1889 (2), 40, 257; 1890 (2), 42, 184; see also Nietzki and Schneider, *Ber.*, 1894, 27, 1481.

tion of oximes from aromatic ketones. Neither phenylmesitylketone, xylol-*o*-tolylketone nor benzpinacolone react with hydroxylamine.¹



Many examples of the same kind have been recently brought to light by Baum and V. Meyer.² It should, however, be pointed out that the nature of the second radical attached to the ketone group also influences the result, for both mesityl aldehyde and mesitylglyoxylic ester readily form oximes.



From the close analogy existing in structure and mode of formation between the hydrazones and oximes, similar results might be looked for in the action of phenylhydrazine, an anticipation which experience has fully justified. The presence of ortho substituents retard or prevent the reaction in precisely the same way. On the other hand mesitylglyoxylic acid, and especially its dinitro derivative, unite with this reagent.³

A further example of interference is afforded by the well-known reaction between aromatic aldehydes and primary aromatic amines, which give rise to benzalanilines. Hantzsch found that the reaction does not occur with symmetrical tribromo- and trinitro-aniline.⁴

¹ Hantzsch, *Ber.*, 1890, 23, 2778; Smith, *Ber.*, 1891, 24, 4050; Beckmann and Wegerhoff, *Annalen*, 1889, 252, 14; Harries and Hübner, *Annalen*, 1897, 296, 301.

² *Ber.*, 1896, 28, 8307; 1896, 29, 886, 2564.

³ *Annalen*, 1891, 264, 144.

⁴ *Ber.*, 1890, 23, 2776.

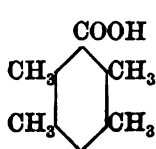
Furthermore, the formation of hydrazones of benzaldehyde with ortho-substituted hydrazines, such as *o*-hydrazinebenzoic acid,



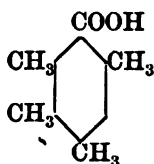
is prevented, whilst the corresponding meta-compound readily combines.

Victor Meyer's Esterification Law. The majority of the foregoing isolated examples of abnormal reactions were known when, in 1894, V. Meyer drew attention to a very remarkable case of interference in the formation of esters, which has found expression in his *esterification law*.

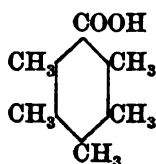
In attempting to prepare the methyl ester of mesitylene carboxylic acid by the action of hydrochloric acid on a mixture of alcohol and acid in the cold, no ester was formed, although the same process produced a nearly theoretical yield in the case of benzoic and its monomethyl, 3:5-dimethyl (mesitylenic acid) and 3:4:6-trimethyl (durylic acid) derivatives.¹ This did not arise from any inability on the part of mesitylene carboxylic acid to form an ester, for it was readily obtained from the silver salt by the action of the alkyl iodide. This observation was followed by the discovery that durene carboxylic, isodurene carboxylic, and pentamethyl benzoic acid, all of which contain methyl groups in both ortho positions to the carboxyl, share the property with mesitylenic acid in yielding no ester with hydrochloric acid in the cold.



Durene
carboxylic acid.



Isodurene
carboxylic acid.



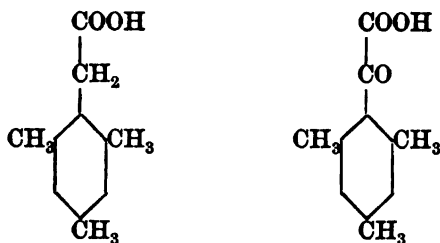
Pentamethyl
benzoic acid.

The same thing was found to occur with diortho-substituted chloro-, bromo-, and nitro-benzoic acids, which formed no ester, whilst similar compounds with at least one free ortho position yielded the ester without difficulty.

That the inactivity of the ortho-substituted acids arises from the position occupied by the groups rather than from their chemical nature, is evident from the similar effect produced by both positive

¹ *Ber.*, 1894, 27, 510, 1580; 1895, 28, 1255, 2774, 8197; see also Gattermann, *Ber.*, 1899, 32, 1117.

alkyl and negative halogens and nitro groups. That the interference is further determined by steric conditions seems probable from the behaviour of both mesityl acetic and mesityl glyoxylic acid (in which the carboxyl is removed from the proximity of the two methyl groups), for, unlike mesityl carboxylic acid, they readily yield esters.



These preliminary observations led V. Meyer and his pupils to a more elaborate quantitative examination of the phenomenon. In estimating the amount of ester formed at a given temperature they adopted the method of Fischer and Speier, which consists in heating the acid with methyl alcohol containing 2 or 3 per cent. of hydrogen chloride for a definite time. In this way it became possible to determine the relative rate of esterification in cases where the process was not prevented, but merely retarded.

Kallas¹ estimated the relative quantity of ester of ortho-, meta-, and para-isomers of mono-substituted benzoic acids formed at different temperatures, and although he found the rate of esterification to increase with rise of temperature, the ortho compound always yielded the smallest amount of ester. The following examples, which represent the percentage of acid esterified in two hours at 51°, illustrate the point in question :

	CH ₃	Cl	Br	I	NO ₂
<i>o.</i>	48.8	50.9	48.4	20.5	8.6
<i>m.</i>	77.1	72.0	66.6	57.6	57.1
<i>p.</i>	75.6	70.5	61.0	52.9	57.1

Benzoic acid = 82.5.

The results agree with the velocity constants (K) of esterification which were ascertained by Goldschmidt.² The reaction between acid and alcohol is bimolecular, but if the quantity of alcohol is large in proportion to the acid, the former may be regarded as constant in quantity, whilst the influence of the small amount of hydrochloric acid (2 per cent.), which acts the part of a catalyst, is too insignificant to be regarded. The reaction, therefore, resolves itself

¹ *Zeit. phys. Chem.*, 1897, 24, 221.

² *Ber.*, 1895, 28, 3218.

into a unimolecular one, and the velocity constant may be determined from the usual equation for a unimolecular non-reversible reaction,

$$k = \frac{1}{t} \log \frac{a}{a-x}$$

in which k is the velocity constant, t the time, a the concentration of the acid at the beginning, and x the amount of ester formed in time t . By heating at constant temperature and withdrawing a portion of the mixture at intervals, the quantity of ester formed can be rapidly estimated by titrating the free acid. The following are some of the numbers obtained for k :

	CH ₃	Br	NO ₂
<i>o</i> .	0.0111	0.0208	0.0028
<i>m</i> .	0.0470	0.0558	0.0296
<i>p</i> .	0.0241	0.0450	0.0261

Benzoic acid = 0.0428.

Attention is drawn to the fact that in both series of determinations the effects of meta- and para-substitution are not equivalent, and the greater esterification values in the case of the meta-compounds points to the existence of other factors in the phenomenon of interference which cannot be disregarded in seeking for a complete explanation. The relative amount of esterification of different diortho acids has also been the subject of a careful study by V. Meyer.¹ He found, for example, that no esterification took place in twelve hours at 0°, or by Fischer and Speier's method in the case of thymotic, *o*-phenylsalicylic, mesitylene carboxylic, and other diortho acids in which both ortho hydrogen atoms are replaced by hydroxyl or methyl groups; but that if hydrochloric acid gas is passed into the boiling alcoholic solution for several hours, the following percentage of ester was formed,

Thymotic acid	28.8
<i>o</i> -Phenylsalicylic "	76.5
Mesitylene carboxylic "	64.5
Pentamethyl benzoic "	70
Durene carboxylic "	60

whereas symmetrical trichloro-, tribromo-, trinitro-, and 2:6-dibromobenzoic acids under similar conditions remained unchanged. Van Loon and V. Meyer² have also shown that 2-fluoro-6-nitrobenzoic acid gives 2 per cent. of ester on standing for twelve hours at 0°, that is, under conditions which in the case of benzoic acid yield 97 per cent. of ester, whilst V. Meyer found that even the ortho hydrogen atoms in benzoic acid diminish the amount of ester, inasmuch as

¹ *Ber.*, 1895, 28, 1254.

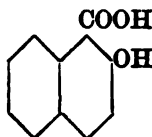
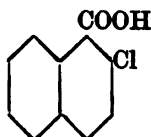
² *Ber.*, 1896, 29, 889.

phenylacetic acid is more rapidly esterified than benzoic acid. It would, therefore, appear that whilst hydrogen, fluorine, hydroxyl, and methyl retard esterification, to a greater or less extent, it is only completely arrested by chlorine, bromine, iodine, and nitro groups. V. Meyer draws the conclusion that the atomic weights or size of the groups which prevent esterification in the hot liquid are much larger than those which only produce this effect in the cold.¹

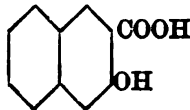
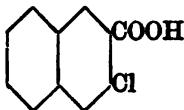
<i>Retard.</i>	<i>Prevent.</i>
H = 1	Cl = 35.4
CH ₃ = 15	NO ₂ = 46
OH = 17	Br = 80
F = 19	I = 127

This view cannot be strictly maintained; for it has been shown that little, if any, difference is effected by substituting a larger alkyl radical for methyl, and moreover there is little doubt that in spite of its comparatively small atomic weight, the nitro group has a much more powerful effect than the other three halogens of the second column in preventing esterification.²

A further interesting observation on the rate of esterification is the effect produced by an adjoining nucleus. From the fact that both β -chloro- and β -hydroxy- α -naphthoic acid cannot be esterified in the cold,



whereas β -chloro- and β -hydroxy- β -naphthoic acid behave like benzoic acid,



it follows that the CH group of the adjoining nucleus behaves like an ortho substituent.³

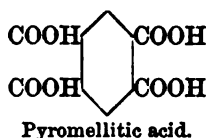
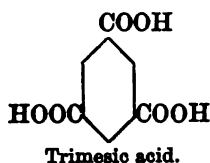
The effect of ortho carboxyl groups on the rate of esterification appears from the behaviour of the polycarboxylic acids to resemble

¹ Ber., 1895, 28, 1260.

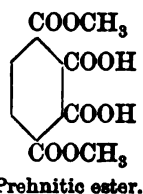
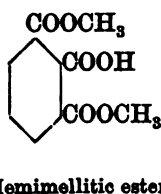
² Kellas, *Zeit. phys. Chem.*, 1897, 24, 221.

³ Ber., 1895, 28, 1254.

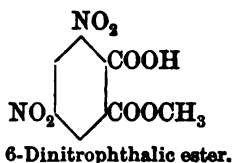
generally that of the other groups.¹ Whilst trimesic and pyromellitic acid give a nearly quantitative yield of ester in the cold,



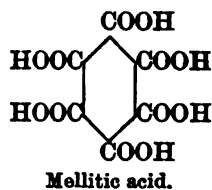
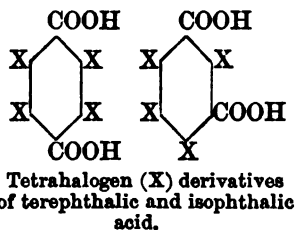
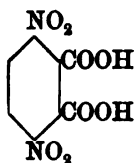
hemimellitic and prehnitic acid give a dimethyl ester.



3-Nitro- and 4:6-dinitrophthalic acids yield chiefly monoalkyl esters,



whilst 3:6-dinitrophthalic acid, the tetrahalogen derivatives of terephthalic and isophthalic acid and also mellitic acid form no ester at all.²



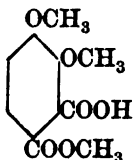
On the other hand, the tetrahalogen derivatives of phthalic acid and 3:6-dichlorophthalic acid, as well as 3:6-dichloro-2-benzoylbenzoic acid and tetrachloro-2-benzoylbenzoic acid³ do not obey the esterification law, inasmuch as they form monoalkyl esters. Another exception is the 3-nitrophthalic acid, which, according to Marckwald

¹ Ber., 1894, 27, 1580.

² Ber., 1894, 27, 8146.

³ Graebe, Ber., 1900, 33, 2026.

and McKenzie,¹ forms with amyl alcohol a little α -monoamyl ester in addition to the β -compound. Also hemipinic acid, which forms an acid ester in the first instance,



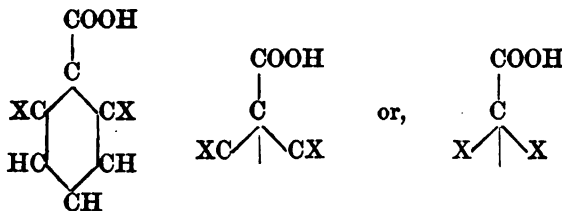
Hemipinic monomethyl ester.

can be converted by prolonged esterification into the neutral compound.

We may conclude then that the carboxyl or carbalkoxyl group, in spite of its atomic weight, resembles the members of the alkyl and hydroxyl series, rather than those of higher atomic weight, seeing that its effect is to retard rather than prevent esterification.

From the results of the above investigation V. Meyer formulated the following law: 'When the hydrogen atoms in the two ortho positions to the carboxyl in a substituted benzoic acid are replaced by radicals, such as, Cl, Br, NO₂, CH₃, COOH, an acid results which can only be esterified with difficulty or not at all.'

The Esterification Law applied to Fatty Acids. The interesting results which have been derived from the study of the aromatic acids suggested a similar behaviour on the part of substituted fatty acids which possess a structure analogous to the diortho compounds of the aromatic series.



In other words, it seemed not unlikely that di- and tri-substituted acetic acids would be influenced by the esterification law. Menshutkin in 1879² showed that the rate of esterification of the mono-, di-, and tri-methyl acetic acids rapidly decreases in the order given when alcohol and acid are heated together in the absence of hydrogen chloride (autocatalysis). Lichty³, using the same method,

¹ Ber., 1901, 34, 486.

² Annalen, 1879, 195, 384; 197, 193.

³ Amer. Chem. J., 1895, 17, 27; 1896, 18, 590.

found that the increase in the number of chlorine atoms facilitated esterification. The subject has received a much more thorough treatment at the hands of Sudborough and his colleagues,¹ who have determined, by the method employed by Goldschmidt, the esterification constants (p. 230) of a long series of substituted acetic acids in presence of hydrochloric acid. The following are the results obtained, in which E stands for the esterification constant for ethyl alcohol at 14.5° and K for the dissociation constant determined by Ostwald and others.

Acid.	Formula.	E.	K.
Acetic	CH ₃ .COOH	3.661	0.00180
Propionic	CH ₃ .Me.COOH	3.049	0.00184
Monochloroacetic	CH ₂ .Cl.COOH	2.433	0.155
Phenylacetic	CH ₂ .Ph.COOH	2.068	—
Bromoacetic	CH ₂ .Br.COOH	1.994	0.183
Iodoacetic	CH ₂ .I.COOH	1.718	0.075
Isobutyric	CHMe ₂ .COOH	1.0196	0.00144
Trimethylacetic	CMe ₃ .COOH	0.0909	0.000973
Dichloroacetic	CHCl ₂ .COOH	0.0640	5.14
Diphenylacetic	CHPh ₂ .COOH	0.05586	—
Dibromoacetic	CHBr ₂ .COOH	0.0510	—
Trichloroacetic	CCl ₃ .COOH	0.0372	121.0
α-Bromoisobutyric	CMe ₂ .Br.COOH	0.0356	—
αα-Dibromopropionic	CMeBr ₂ .COOH	0.0242	3.8
Tribromoacetic	CBr ₃ .COOH	0.01845	—

The experimental evidence clearly indicates that the rate of esterification is retarded in proportion to the number and size of the atoms or groups introduced into the acetic acid molecule, and is independent of the strength of the acid as determined by its dissociation constant. Similar influences therefore affect the esterification of both fatty and aromatic acids. Other contributions to the subject of esterification have only served to demonstrate the steric effects which underlie the process. One investigation by Sudborough and Lloyd has reference to unsaturated acids of the acrylic series, of the formula CHX : CY . COOH and CXY : CZ . COOH,² all of which can exist in cis and trans configurations. Cis acids of both the above formulae are difficult to esterify by Fischer and Speier's method, whilst the corresponding trans acids are readily converted into esters.

A second paper³ by Bone, Sudborough, and Sprankling on the esterification of the mono esters of the methyl succinic acids 'affords another example of the retardation induced by the successive intro-

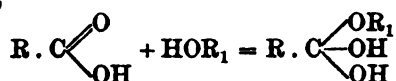
¹ *Trans. Chem. Soc.*, 1899, 75, 467.

² *Trans. Chem. Soc.*, 1898, 73, 81.

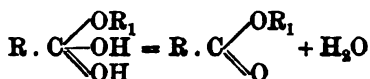
³ *Trans. Chem. Soc.*, 1904, 87, 584.

duction of methyl groups'. Also, Blaise¹ has shown that in *as*-dimethylsuccinic acid the tertiary carboxyl is more difficult to esterify than the primary group.

From what has been already stated of the absence of any relation between the dissociation constants and rate of esterification (p. 234), it is clear that the process is not determined by the presence of free ions. The explanation suggested by Wegscheider² assumes that the ester formation is preceded by the addition of a molecule of alcohol and acid,



from which water is then removed.



This view finds some confirmation in the fact that whilst benzoic ester forms an additive compound with sodium methoxide, mesitylenic ester does not.

It is easy to conceive that the presence of large groups or atoms in the neighbourhood of the carboxyl of the acid molecule would interfere with the interaction of the alcohol molecule by preventing the formation of the additive compound.

An apparent contradiction of this view is the formation of acetals (by the action of aldehydes on alcohols in presence of hydrochloric acid) which was studied by E. Fischer and Giebe,³



for ortho-substituted aldehydes like 2:5-dichloro- and 2-nitro-3:6-dichloro-benzaldehyde react more readily than the unsubstituted compound itself; but this may be merely an example of steric hindrance neutralized by the specific effect of acidic groups, which, like nitro groups in the hydrolysis of esters (p. 236), and of ortho-substituted cyanides (p. 237); in the reduction of nitro compounds (p. 241) and in the formation of hydrazones (p. 227), assist the reaction.

Hydrolysis of Esters. If the esterification law is based on steric hindrance, similar influences might be expected to underlie the rate of ester hydrolysis. Such indeed is the case, although there are notable differences in the character of ester formation and hydrolysis, to which attention will be drawn. The rate of hydrolysis of mono-

¹ *Compt. rend.*, 1898, 126, 753.

² *Monatsh.*, 1895, 16, 148.

³ *Ber.*, 1898, 31, 545.

substituted benzoic esters was examined first by V. Meyer¹ and then more thoroughly by Kellas², who found that substitution in the ortho position hinders the process more than in the meta- or para-position; but whilst methyl in the two latter positions retarded hydrolysis as compared with benzoic ester, the presence of the halogens and still more of the nitro group increased it, so that the absolute rate of hydrolysis of both the mono-halogen and mono-nitro substituted benzoic esters is in many cases greater than that of benzoic ester itself. But as a rule the general effects of ester hydrolysis run parallel with those of esterification, and in most cases the esterification law enables us to predict the result.

Thus the ortho-substituted esters of α -naphthoic acid are more difficult to hydrolyse than those of the β -compound; in the mono-halogen or mono-nitroterephthalic esters the ester group in the meta position to the substituent is first attacked; the same happens with the nitrophthalic esters, in which hydrolysis of the ester group farthest from the nitro group takes precedence. An explanation such as V. Meyer applied to esterification may be repeated here, for the molecule of alkali may form an additive compound with the ester previous to the rupture of the alcohol molecule.

Hydrolysis of Amides and Acyl Chlorides. The steric influences which retard hydrolysis underlie the formation or non-formation of amides when ammonia acts on esters, and the same phenomenon has been observed in the hydrolysis of ortho-substituted acid chlorides, cyanides, and amides, as well as in the action of alcohols on acid chlorides. Fischer and Dilthey studied the first reaction in the case of the series of alkyl malonic esters,³ whilst V. Meyer,⁴ Sudborough and his collaborators, and also Claus investigated the hydrolysis of acid chlorides, amides, and cyanides of the benzene series. Fischer and Dilthey found that not only did the presence of dialkyl groups in malonic ester retard the formation of amides, but that diethyl and dipropylmalonamide were more slowly hydrolysed than the parent substance. From a study of the acid chlorides Sudborough⁵ concludes that those in which substitution does not occur in either of the ortho positions are readily decomposed by dilute alkalis, whereas those which have a bromine atom in one ortho position are relatively more stable, but where both ortho positions are occupied by bromine atoms the compounds are remarkably stable and are only converted into the corre-

¹ Ber., 1895, 28, 188.

² Ber., 1902, 35, 844.

³ Trans. Chem. Soc., 1895, 67, 601.

⁴ Zeit. phys. Chem., 1897, 24, 248.

⁵ Ber., 1894, 27, 3158.

sponding sodium salts of the acids by long continued boiling with an alkali solution.

It has already been mentioned that Claus and his pupils in 1891 and 1892 observed the difficulty with which ortho-substituted benzamides undergo hydrolysis. The subject attracted fresh interest after the discovery of the 'esterification law', and Sudborough, in conjunction with Jackson and Lloyd,¹ submitted the process to a more searching examination. The hydrolysis was effected with 80, 50, or 75 per cent. sulphuric acid at 160°, or at the boiling-point, and a comparison made of the quantities of acid formed in a given time. The results conclusively showed that ortho-substituted derivatives strongly retarded the process, so that under conditions which effected almost complete hydrolysis of 3:5 and 2:4-dibromobenzamide only 11 per cent. of 2:6-dibromo and 4.5 per cent. of 2:4:6-tribromobenzamide were converted. Of the same nature are the constants obtained by Remsen and Reid² of the comparative rates of hydrolysis of ortho-, meta-, and para-substituted benzamides in which the retarding effect of the ortho substituent is very evident.

Hydrolysis of Cyanides. That the cyanides should behave like amides on hydrolysis is a natural conclusion which the observations of Claus and others on the hydrolysis of substituted benzonitriles, referred to in the earlier part of the present chapter, have served to confirm. The subject is reopened merely to draw attention to the influence of the nitro group in this reaction, for it is not a little significant that the presence of one, still more of two, nitro groups greatly facilitates hydrolysis. Whilst great difficulty is experienced in hydrolysing *symm*-trimethylbenzonitrile the mono- and dinitro-derivatives may be completely, though slowly, converted into acids.³ It is clear, therefore, that the nitro group plays a special rôle in modifying steric influences, a fact which also becomes evident in the rate of reduction of nitro compounds (p. 241).

Action of Alcohols on Acid Chlorides. Steric influences also determine the union of acid chlorides with alcohols, and among the series of menthyl esters of disubstituted benzoyl chlorides obtained by the writer and his collaborators,⁴ it was invariably found that the diortho compound requires a much higher temperature and more

¹ *Trans. Chem. Soc.*, 1895, 67, 601; 1897, 71, 239.

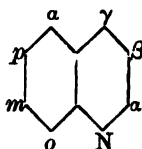
² *Amer. Chem. J.*, 1899, 21, 840.

³ Küster and Stallberg, *Annalen*, 1894, 278, 207.

⁴ *Trans. Chem. Soc.*, 1906, 89, 1482.

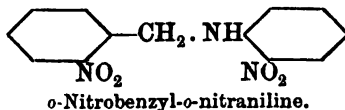
prolonged heating than the other acid chlorides to effect combination with menthol.

Formation of Alkylammonium Iodides. Reference has already been made to Hofmann's observation that certain tertiary aromatic amines refuse to combine with alkyl iodide to form quaternary compounds. The subject was reinvestigated by Fischer and Windaus,¹ who showed that it was clearly the effect of steric hindrance. For of the six isomeric xylidines, though they can be converted into tertiary bases by Noelting's method (using methyl iodide and sodium carbonate), it is only the 2:6-compound which gives no quaternary ammonium iodide. The same is the case with the different isomeric bromotoluidines and bromoxylidines. Moreover, Friedländer² found that 2:6-xylidine can, with difficulty, be converted into the tertiary diethyl compound, whilst Effront³ could only obtain traces of the dimethyl tertiary base with 2-methyl-6-isobutyl toluidine and methyl iodide at 150°. Decker drew attention to the same phenomenon in connection with the *o*- or *α*-substituted quinolines,



which, like the diortho xylidines or bromotoluidines, will not combine with alkyl iodides.

Acetylation of Secondary Bases. Paal and Kromschroder⁴ have shown that not only does *o*-nitrobenzyl chloride react with difficulty to form *o*-nitrobenzyl-*o*-nitraniline when the *m*- and *p*-compounds readily unite, but that the product obtained is proof against acetylation.



Furthermore, of the compounds obtained by combining *p*-nitrobenzyl chloride with the three isomeric nitranilines, only the *o*-nitraniline derivative resists the introduction of the acetyl and formyl group. It follows, therefore, that the ortho-nitro group of the base controls the action, and from the fact that *o*-nitrobenzyl-*o*-anisidine

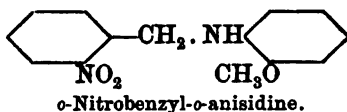
¹ *Ber.*, 1900, 33, 345, 1967.

² *Ber.*, 1884, 17, 2817.

³ *Monatsh.*, 1898, 19, 645.

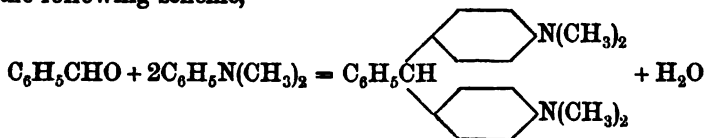
⁴ *J. prakt. Chem.*, 1896, 54, 265.

gives a formyl derivative, it would seem that this action is determined by the negative character of the group.



Action of Nitrous and Nitric Acid and Diazo-salts on Aromatic Amines. Steric hindrance also appears to modify the action of nitric and nitrous acid and diazo compounds on ortho-substituted secondary and tertiary bases. Thus dimethyl-o-toluidine and o-methoxy-dimethyl aniline, unlike dimethyl aniline, give no nitroso derivatives, although the para position is free. Similarly o-substituted dialkyl or acetalkyl anilines give meta- and not para-nitro derivatives. Diazobenzene chloride, which readily forms an aminoazo compound with dimethyl aniline, reacts with difficulty when an ortho-substituted dialkyl aniline is present. In these cases the ortho substituent is supposed to influence the initial formation of an additive compound which is assumed to occur between the nitrogen of the tertiary base and the reagent previous to substitution in the nucleus.

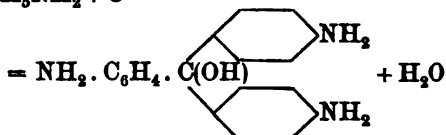
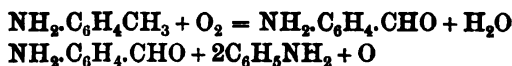
Action of Benzaldehydes on Aromatic Amines. The same explanation may serve to explain the non-formation of triphenyl-methane derivatives when union between aldehydes and o-substituted tertiary bases is attempted. The reaction, which occurs according to the following scheme,



is effected by attachment of the aldehyde carbon to the para-carbon atom of the amine, and there is no obvious reason why ortho substitution should produce steric hindrance unless some kind of additive compound with the tertiary nitrogen is assumed.

If, in place of a tertiary amine, a primary aromatic amine is substituted, it is the *m*-substitution which hinders the reaction. Whilst o-toluidine reacts readily with *p*-nitrobenzaldehyde, the *m*-compound does so with difficulty. We must suppose here that the aldehyde carbon attaches itself directly to the para-carbon of the nucleus. That the reactions with primary and tertiary bases should afford so curious a contrast in behaviour is somewhat striking.

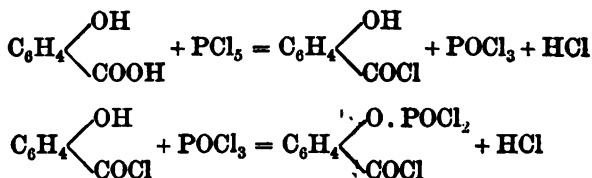
Formation of Rosanilines. The difficulty of combining aldehydes with meta-substituted bases reappears in the formation of the rosanilines, in which *p*-toluidine is oxidized in presence of primary aromatic amines, a reaction which in reality resolves itself into a combination of aldehyde and amine, thus :



In the example given, both *p*-toluidine and aniline may be replaced by other amines ; but Noelting has shown that if, in place of aniline, meta-amines like *m*-toluidine and symm-*m*-xylydine are substituted, the reaction does not take place. The reason from the stereochemical standpoint is clear enough, when we consider that the methyl group in the meta position to the carbon stands in the ortho-position to the para-carbon with which the aldehyde group always interacts. The argument might be advanced that rosaniline derivatives, having meta-substituted groups are incapable of existence, but this is met by the fact that indirect methods have been successfully used in their preparation.

Many other examples of steric hindrance might be given, but we shall limit ourselves to two more : the action of phosphorus pentachloride on hydroxy-acids, and of ammonium sulphide on nitro compounds.

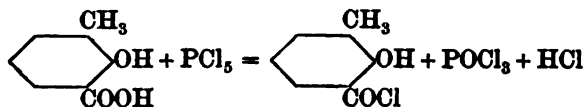
Action of Phosphorus Pentachloride on Hydroxy-acids. Anschütz¹ and his pupils have shown that the ordinary course of the reaction between phosphorus pentachloride and hydroxy-acids is usually presented by the following two equations :



If, however, the two ortho positions to the hydroxyl are occupied as

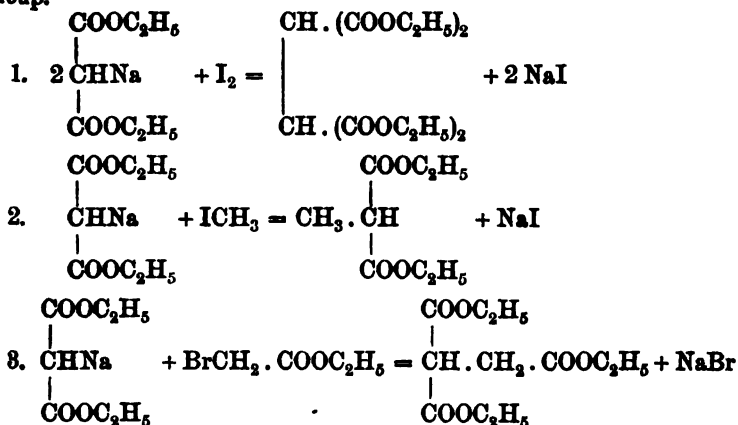
¹ Ber., 1897, 30, 221.

in *o*-methylsalicylic acid, the phosphorus oxychloride produces no change in the hydroxyl group.



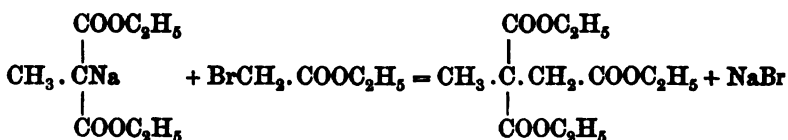
Reduction of Nitro Compounds. The writer, in conjunction with D. McCandlish, studied the action of ammonium sulphide on a variety of substituted nitro derivatives of benzene.¹ It was invariably found that, although the presence of acidic groups facilitates reduction, the nitro group was more slowly attacked by the reducing agent if it occurred in the ortho position to a methyl or ester group, than when present in the meta or para position.

Bischoff's 'Verkettungen'. The subject of steric hindrance would scarcely be complete without some reference to the enormous mass of detailed research which has been accumulated by Bischoff and his collaborators on *Verkettungen* or conditions affecting the linking of simply constituted compounds. We cannot pretend to sift the whole of the materials, but we may point out that steric influences as factors determining chemical change are throughout clearly in evidence. A few examples must suffice. Sodium malonic ester readily reacts with halogens, alkyl halogens, and halogen esters, and the process may often be repeated by introducing a second sodium atom and halogen group.

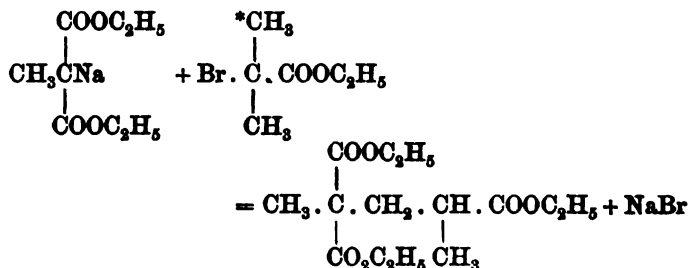


Nos. 2 and 3 may be combined by introducing an acetic ester group into methyl malonic ester.

¹ *Trans. Chem. Soc.*, 1905, 87, 1257.



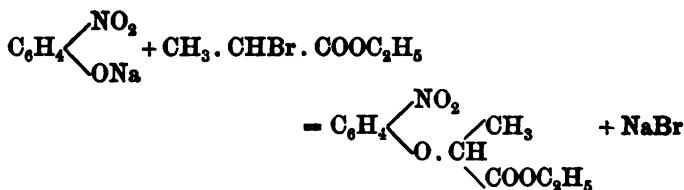
Steric influences begin to assert themselves in the last reaction as soon as larger alkyl groups are introduced into the malonic ester molecule on the one hand, or the α -bromine atom in the halogen ester is replaced by one forming a tertiary group. For example, if sodium methyl malonic ester and α -bromo isobutyric ester are boiled together in alcoholic solution, the reaction proceeds abnormally in the following manner, in which, instead of the α -carbon, $^*\text{C}$ becomes linked to the malonic ester molecule.



In xylene solution, however, the reaction takes its normal course.

Also, in such a case as the linking of sodium phenates and halogen esters, steric influences may modify the result.

Whilst sodium *o*-nitrophenate and α -bromopropionic ester combine in a normal fashion,



no reaction occurs with α -bromoisobutyric ester.

In reviewing the foregoing results it must be admitted that a strong case has been made out for the principle of steric hindrance. At the same time a fact, which has been frequently emphasized, must not be overlooked; namely, the specific nature of the group or groups present in the compound resists certain expected changes. In illustration of this, it has been pointed out by Stewart¹ that the

¹ *Trans. Chem. Soc.*, 1905, 87, 185.

formation of bisulphite compounds of ketones is determined by the nature of the radicals attached to the ketone group; that whilst the increase in the size of the hydrocarbon radical retards, the presence of carboxyl facilitates bisulphite formation. This reactivity has been attributed, not to effects of steric hindrance, but to *potential tautomerism*, a property which is supposed to be manifested by absorption bands in the ultra-violet (see p. 207).¹

Again, Auwers and Perkin find that, whereas methylacrylic acid condenses readily with sodium malonic ester, dimethylacrylic acid gives a very small yield, and trimethylacrylic acid refuses to react. This may be merely a case of the positive alkyl groups affecting the whole character of the compound and not necessarily one of interference, just as the additive power of olefines for bromine is diminished by the attachment of negative groups, such as carboxyl, ester and phenyl groups, or bromine atoms to the doubly linked carbons. The concurrent influences of position and character of the group are not always easy to differentiate, but for that very reason the conclusion that an apparently anomalous reaction is to be placed to the account of steric influences should be made with caution.

It must be confessed that we are still profoundly ignorant of the change which substituents effect in the character of the molecule as a whole, the causes which determine the rules of orientation, the reason why positive groups like methyl and amino groups facilitate nitration, sulphonation, acetylation by the Friedel-Crafts' method,² &c., why negative groups assist hydrolysis of cyanides, reduction of nitro groups, acetal formation, &c., and a host of other phenomena of a similar nature. Until clearer views obtain on these subjects it can scarcely be hoped that real progress will be made on the nature of chemical change. The expression 'steric hindrance' will meantime afford a useful and quite appropriate title for docketing a number of allied phenomena.

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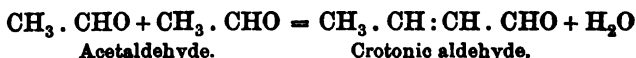
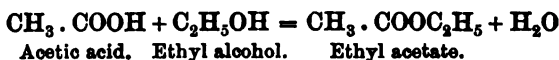
¹ *Trans. Chem. Soc.*, 1906, 89, 439.

² V. Meyer, *Ber.*, 1896, 29, 1418, 2564; Kunckell and Hildebrandt, *Ber.* 1901, 34, 1826.

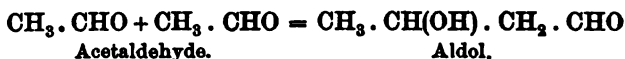
CHAPTER VII

CONDENSATION

THE terms *condensation* and *condensation product* imply a process and its result which have never been clearly defined, but which at the same time convey a distinct idea. Thus, the combination of ethyl alcohol and acetic acid to form an ester—a reaction in which water is separated—would not be termed condensation, yet the union of two molecules of acetaldehyde to form crotonic aldehyde, in which water is likewise removed, would be regarded as a typical example of such a process.



Again, all reactions of which the conversion of aldehyde into aldol may be taken as the type are termed *aldol condensations*; but in this case no water is separated.



It is easy to draw a distinction between the formation of acetic ester from alcohol and acetic acid and that of crotonic aldehyde from acetaldehyde. In the first reaction the two molecules are linked in the new product by oxygen, and are again readily separated by hydrolysis; but in the second reaction the new linkage is established between carbon atoms, and the product is consequently of a much more stable character. This might help us to a definition, were it not that in the third example no water is eliminated, although the new combination is effected between carbon atoms.

Although it is true that the formation of aldol is covered by the term *polymerisation*, and should, strictly speaking, be included in this category, yet it is distinct from the process which gives rise to paraldehyde, a compound which, unlike aldol, is readily dissociated into the original aldehyde. In other words, the one is a reversible, the other is practically a non-reversible process.

As the formation of aldol is intimately linked with that of crotonic aldehyde, it would be illogical to draw distinctions between the two processes and the term *aldol condensation* is therefore justified.

Condensation may, then, be defined as the union of two or more organic molecules or parts of the same molecule, with or without elimination of component elements, in which the new combination is effected between carbon atoms.

If this definition is accepted it will naturally embrace every kind of reaction in which new organic compounds are elaborated by the linking of carbon atoms. Used in this sense the word condensation can be conveniently applied to denote a certain section of the more comprehensive category of constructive chemical changes which are included in the term *synthesis*.

There is no intention of implying that the combination between carbon atoms is subject to different conditions from those obtaining among other elements. The union is as a rule more stable, but not necessarily so, and many reversible changes are known, in which the carbon atoms part company as well as combine. It must be recognized that the distinction is artificial and merely convenient. Also, for convenience, it is desirable to distinguish between *external condensation*, in which two or more different molecules become linked together and *internal condensation*, in which carbon atoms in the same molecule combine.

The process of condensation is connected with the early history of organic chemistry, and was the outcome of the first systematic attempts at organic synthesis.

In the following pages it is intended to give a general survey of the principal condensation processes.

Metallic Reagents. It was in the pursuit of the free radicals that Frankland first used potassium and the alkyl cyanides, which in 1849 he replaced by zinc and the alkyl iodides (p. 85).¹

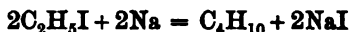
This inquiry resulted in two discoveries of the highest importance—the synthesis of the paraffins and the production of the first organo-metallic compounds. The method devised by Frankland of using a metal to remove the halogen from an organic halogen compound so as to effect a union between the residual parts of the molecules has undergone a wide extension.

The Method of Wurtz. In 1855 Wurtz² introduced sodium in

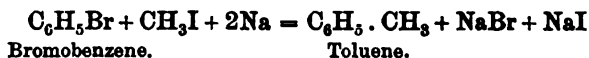
¹ *Phil. Trans.*, 1852, 142, 417; *Annalen*, 1853, 85, 829.

² *Annalen*, 1855, 96, 365.

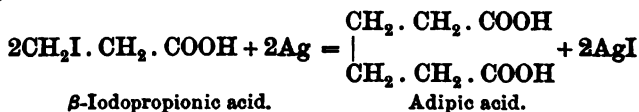
place of zinc for preparing different paraffins from the alkyl iodides, as, for example, butane from ethyl iodide,



and the same method was applied by Fittig¹ in 1863 to the preparation of the homologues of benzene.



In 1868 Wislicenus² employed finely divided metallic silver in the synthesis of dibasic from monobasic acids.



Finely divided copper, although occasionally used in place of silver, has only received extended application as a condensing agent in recent years.³

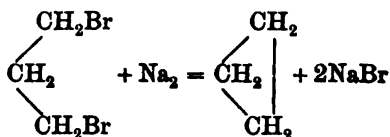
The formation of benzoic ester by Wurtz from bromobenzene, chloroformic ester and sodium,



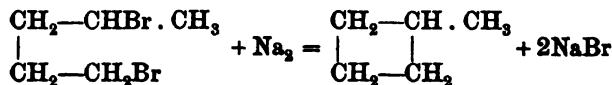
and that of sodium benzoate from bromobenzene, carbon dioxide and sodium by Kekulé⁴ are merely modifications of the same process.



The same principle has been applied by Freund⁵ to the production of ring compounds by internal condensation in the synthesis of cyclopropane from trimethylene bromide and sodium or zinc,



and by Perkin, jun.,⁶ and his collaborators in the synthesis of methyl cyclobutane from 1.4 dibromopentane,



¹ *Annalen*, 1863, 131, 304.

² *Annalen*, 1868, 149, 221; *Ber.*, 1869, 2, 720.

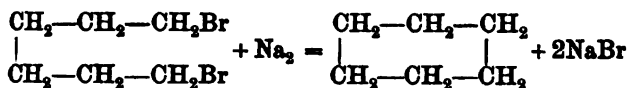
³ Ullmann, *Ber.*, 1903, 36, 2383; 1904, 37, 853; *Annalen*, 1904, 332, 88; *Ber.*, 1905, 38, 729, 2120, 2211.

⁴ *Annalen*, 1866, 137, 180.

⁵ *Monatsh.*, 1882, 3, 625.

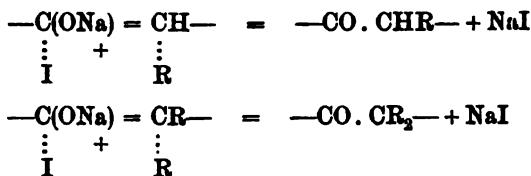
⁶ *Trans. Chem. Soc.*, 1883, 53, 201; 1894, 65, 599.

and cyclohexane from hexamethylene dibromide,



The Method of Wislicenus. The discovery of a series of organic compounds of the nature of 1.3 diketones, such as acetyl acetone, acetoacetic ester, malonic ester, acetone dicarboxylic ester and similarly constituted compounds, cyanacetic ester, benzyl cyanide, desoxybenzoin, &c., which form sodium compounds by the replacement of hydrogen by sodium, gave a new impulse to the study of organic synthesis. The further discovery by Conrad¹ that in the preparation of the sodium compounds, metallic sodium or dry sodium ethoxide could be replaced by an alcoholic solution of sodium ethoxide, added greatly to the convenience of the method. We are not concerned for the moment either with the structure of the sodium compounds, which is discussed under tautomerism (p. 178), or with the mechanism of the formation of the compounds themselves, which finds a place under the acetoacetic ester synthesis (p. 260). Our attention at present will be directed to the description of a few of the more important synthetic operations in which the sodium compounds have been utilized.

If to an alcoholic solution of these compounds containing the equivalent of one atom of sodium, an alkyl iodide is added, and the liquid boiled until neutral, sodium iodide separates, and the alkyl derivative is formed. The process may usually be repeated by adding a second atomic equivalent of sodium in alcohol and a second molecule of alkyl iodide, when the dialkyl derivative is obtained. If these sodium compounds possess, as they admittedly do, the enolic structure, the action of the alkyl iodide must be represented by some such general schemes as the following, in which addition precedes substitution :²



It will be seen that the negative iodine unites with the positive

¹ *Annalen*, 1880, 204, 127.

² Michael, *J. prakt. Chem.*, 1892, 46, 194; 1899, 60, 816; Nef, *Annalen*, 1891, 266, 67, 118; 1892, 270, 330; Thorpe, *Trans. Chem. Soc.*, 1900, 77, 923.

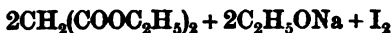
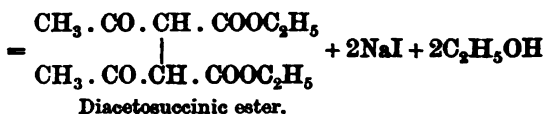
sodium and the positive radical with the carbon which forms part of a negative group.¹ It should be noted in passing that by substituting pyridine for sodium ethoxide as condensing agent the alkyl attaches itself to the oxygen and the isomeric enolic form is produced.

The use of these methods for synthesising acids and ketones from acetoacetic ester and acids from malonic and cyanacetic ester belong to the elementary facts of organic chemistry and need not be discussed in detail.

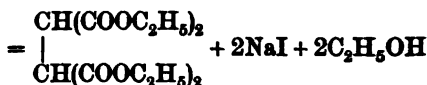
If in place of an alkyl iodide, iodine is added to the alcoholic solution of the sodium compounds, polybasic acids may be obtained from acetoacetic ester and malonic ester as follows (p. 192):²



Acetoacetic ester.

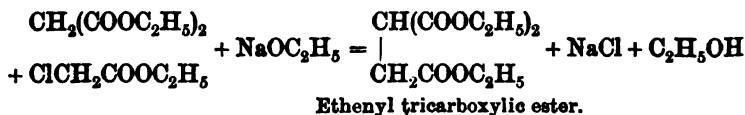
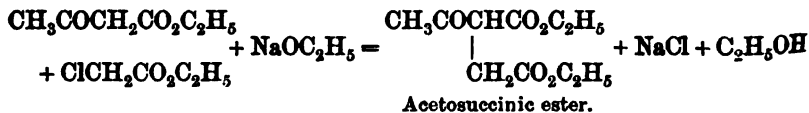


Malonic ester.



Ethane tetracarboxylic ester.

Again, if a halogen derivative of a fatty ester like chloroacetic ester is allowed to interact, a variety of polybasic acids may be prepared, which the following examples will serve to illustrate:³

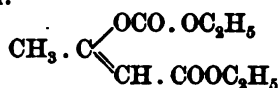


¹ This view is embodied in Michael's 'positive-negative' theory, *J. prakt. Chem.*, 1888, 37, 478.

² Harrow, *Annalen*, 1880, 201, 142; Bischoff and Rach, *Ber.*, 1884, 17, 2781.

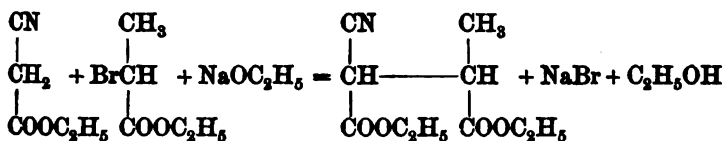
³ Bischoff and Rach, *Annalen*, 1882, 214, 88; 1886, 234, 86; Conrad, *Annalen*, 1877, 188, 218.

Chloroformic ester is an exception to the general rule in producing mainly the enolic ester.

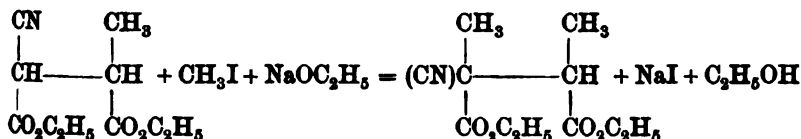


Cyanacetic ester behaves in precisely the same way as malonic ester. To take one example, symmetrical dimethylsuccinic ester has been prepared as follows :¹

By the combined action of cyanacetic ester, α -bromopropionic ester and sodium ethoxide, cyanomethyl succinic ester is first obtained.



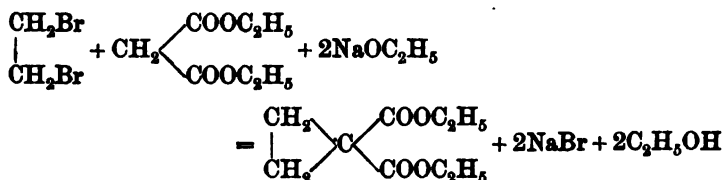
The substance is then boiled up with methyl iodide and sodium ethoxide, when the following change occurs :



Finally, the product is hydrolysed with hydrochloric acid, whereby the cyanogen group is converted into carboxyl and removed as carbon dioxide, yielding symmetrical dimethylsuccinic acid.

The Synthesis of Cyclic Compounds (Perkin's Method). The formation of sodium compounds of 1.3 diketones, more especially of malonic and acetoacetic ester, has found a further important application in the production of cyclic compounds.² The subject can only be briefly outlined.

Ethylene bromide and sodium malonic ester give cyclopropane dicarboxylic ester.

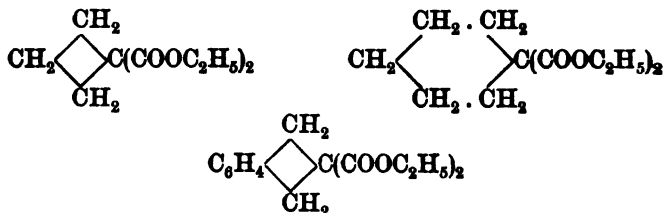


The product when hydrolysed gives the dibasic acid, and, on heating, the corresponding monobasic acid.

¹ Bone and Sprankling, *Trans. Chem. Soc.*, 1899, 75, 889.

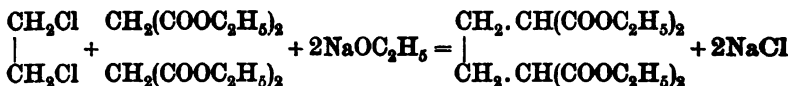
² W. H. Perkin, jun., *Ber.*, 1902, 35, 2091.

In a precisely similar fashion trimethylene bromide, pentamethylene bromide, and *o*-xylylene bromide have been converted into cyclic compounds having the following structure :

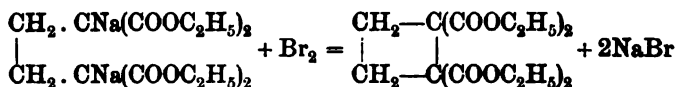


From each of these the corresponding di- and mono-basic acids have been prepared.

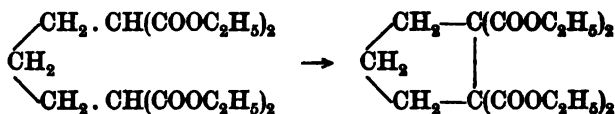
Cyclic formation may also be effected in the following way: ethylene chloride, malonic ester, and sodium ethoxide yield in addition to the cyclic trimethylene compound, already described, an open chain ester.



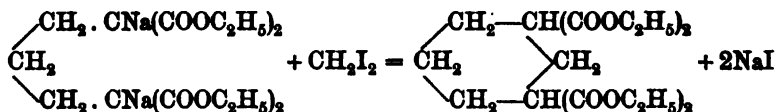
If this butane tetracarboxylic ester is converted into the disodium compound and then treated with bromine or iodine, ring formation occurs.



In place of ethylene chloride trimethylene bromide may be used when cyclopentane tetracarboxylic ester is formed.



Furthermore, by introducing methylene iodide in place of iodine in the last reaction, a cyclohexane derivative is obtained.

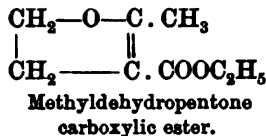
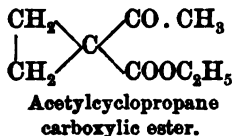


Each of these tetracarboxylic esters may be converted into dicarboxylic acids by the usual process of hydrolysis and heating.

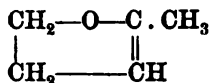
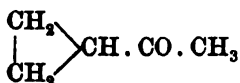
The above series of reactions when applied to acetacetic ester,

benzoylacetic ester, or acetone dicarboxylic ester gives a somewhat different result.

Ethylene bromide, acetoacetic ester, and sodium ethoxide yield not only acetylcyclopropane carboxylic ester, in which the action proceeds normally as in the case of malonic ester, but the enolic form of acetoacetic ester also comes into play, giving an inner ether, methyldehydropentone carboxylic ester.



In the case of trimethylene bromide, the second reaction proceeds to the complete exclusion of the first. On hydrolysis of the above esters, the acid which is formed loses carbon dioxide on heating and gives the following products:



Organo-metallic Compounds. The extraordinary development which organic synthesis owes to the use of organo-metallic compounds has its origin in Frankland's discovery of the zinc alkyl compounds. The preparation of these compounds need not be described. They are extremely unstable liquids which are characterized by their strong affinity for either free or combined oxygen and for the halogens. It is on these properties that their manifold transformations depend. Paraffins may be derived from them either by the direct action of water,¹ of alkyl iodides or dihalogen compounds.² The following reactions illustrate each of the methods:



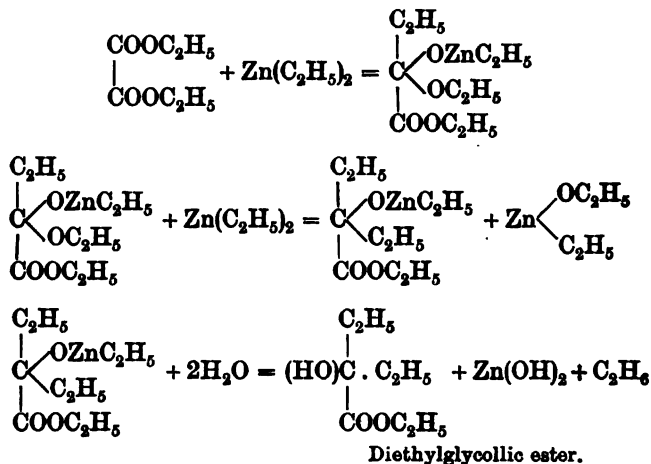
Zinc Alkyl Condensations (Frankland's Method). The discovery by Frankland and Duppa³ of the formation of hydroxy-acid from zinc ethyl and oxalic ester prepared the way for new and unlooked for synthetic uses of the zinc alkyl compounds. If to one

¹ Frankland, *Annalen*, 1849, 71, 203; 1850, 74, 41.

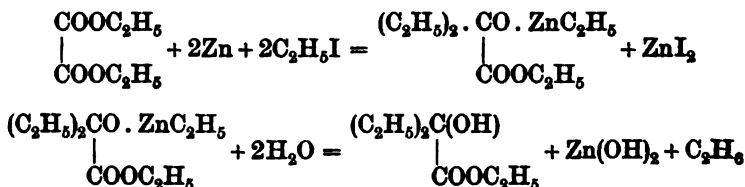
² Friedel and Ladenburg, *Annalen*, 1867, 142, 316; Lwow, *Zeits.*, 1871, 257.

³ *Proc. Roy. Soc.*, 1868, 12, 396; *Annalen*, 1868, 126, 109.

molecule of ester two molecules of zinc alkyl are added and the product decomposed by water, diethylglycollic ester is obtained. The following equations represent the course of the reaction :



The same product was also prepared by heating a mixture of oxalic ester, alkyl iodide, and zinc.¹



This was followed by the researches of Wagner,² on the action of zinc alkyl on aldehydes, which led to the synthesis of secondary alcohols; of Saytzeff,³ who applied a similar reaction to the ketones and obtained tertiary alcohols; of Butlerow,⁴ who prepared alcohols from the acid chlorides; of Freund,⁵ who obtained ketones from the acid chlorides; of Wagner, Saytzeff, and Kannonikoff,⁶ who converted aliphatic esters into secondary and tertiary alcohols. The following examples illustrate the different types of reactions referred to. Aldehydes and zinc alkyls form secondary alcohols. Acetaldehyde and zinc ethyl yield secondary butyl alcohol.

¹ Frankland and Duppa, *Annalen*, 1868, 126, 109; 1868, 125, 26.

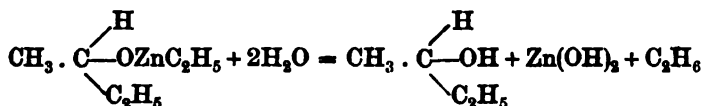
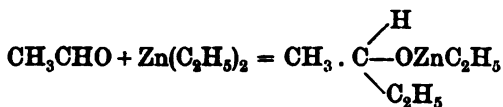
² *Annalen*, 1876, 181, 261.

³ *Annalen*, 1877, 185, 151.

⁴ *Annalen*, 1867, 144, 1.

⁵ *Annalen*, 1861, 118, 3.

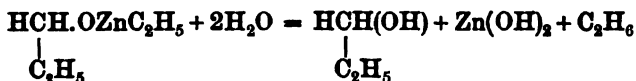
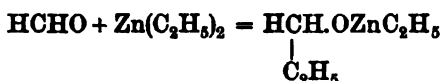
⁶ *Annalen*, 1875, 175, 351; 877, 185, 129, 148, 169.



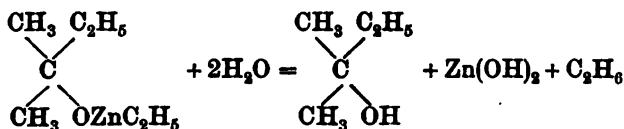
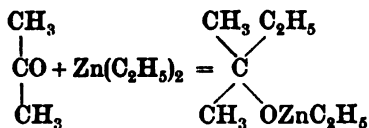
Secondary butyl alcohol.

Formaldehyde gives by a similar series of changes primary alcohols, whereas ketones yield tertiary alcohols.

Formaldehyde and zinc ethyl yield primary propyl alcohol, whilst acetone and zinc ethyl give tertiary amyl alcohol.

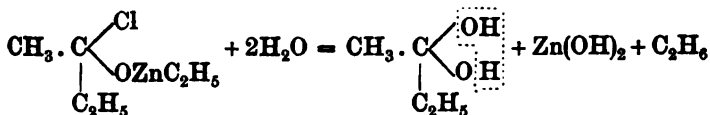
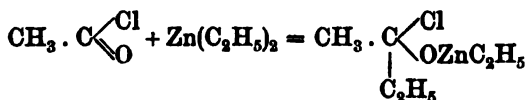


Primary propyl alcohol.



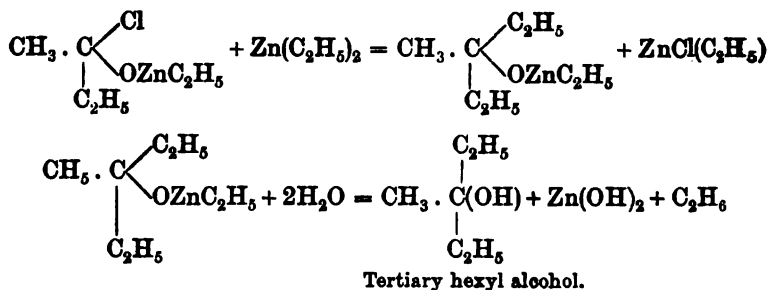
Tertiary amyl alcohol.

Acid chlorides react with one and two molecules of zinc alkyl. Acetyl chloride and zinc ethyl form methyl ethyl ketone.

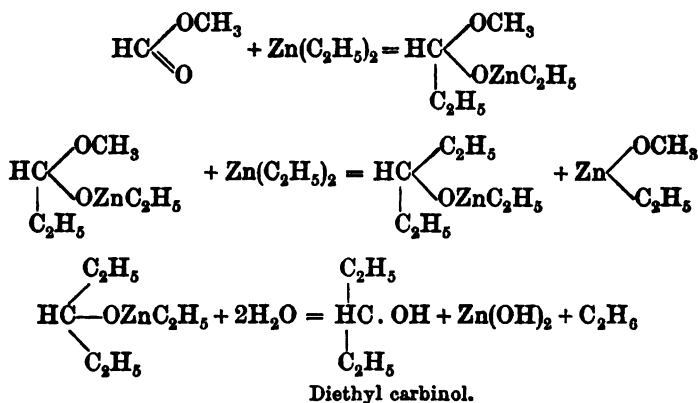


Methyl ethyl ketone.

If the intermediate product is allowed to react with a second molecule of zinc alkyl a tertiary alcohol results.



With the esters a similar process occurs. Methyl formate and two molecules of zinc ethyl yield a secondary butyl alcohol. The reaction occurs in two steps.



Other fatty esters like acetic ester will naturally yield tertiary alcohols by this process.

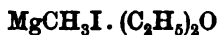
Magnesium Alkyl Condensations (Grignard's Reaction). The use of magnesium in place of zinc for introducing radicals into organic compounds in the manner adopted by Frankland and Duppe was first suggested in 1899 by Barbier,¹ who converted methyl heptenone into a tertiary alcohol by the action of methyl iodide in presence of magnesium. In the following year the study of the preparation and synthetic uses of magnesium alkyl compounds was taken up by Grignard, who published an account of his results in the *Comptes rendus*.² Since then the applications of this method

¹ *Compt. rend.*, 1899, 128, 110.

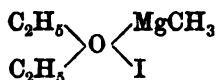
² *Compt. rend.*, 1900, 130, 1322.

have rapidly multiplied.¹ Although the behaviour of the magnesium alkyl compounds will be seen to resemble in many respects that of the zinc alkyls, their greater reactivity, owing no doubt to the more electropositive character of the metal, as well as the convenience of their preparation, offer great advantages over the use of the zinc compounds.

The method of preparation consists in adding to one atomic proportion of clean metallic magnesium wire or ribbon, suspended in perfectly dry ether, a molecular equivalent of the alkyl iodide or bromide (or phenyl or tolyl bromide), also dissolved in ether. The magnesium dissolves with evolution of heat and a solution is usually obtained which contains the magnesium alkyl (or aryl) bromide or iodide. If methyl iodide is used, and, after the action is complete, the excess of ether is evaporated and the product heated in a vacuum to remove the last traces of solvent, the composition of the residue corresponds to a substance of the formula :



According to Baeyer and Villiger the compound is to be represented as containing quadrivalent oxygen.



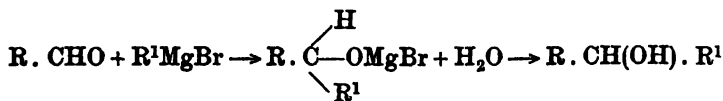
There are reasons for supposing that the ether plays an essential part in the synthetic processes to which the magnesium compound is applied, but discussion of the mechanism of the reaction is reserved until some of its more important applications have been considered.

Hydrocarbons. The magnesium alkyl or aryl iodide is decomposed by water, giving a hydrocarbon.



Alcohols, aldehydes, ketones, and finally acids may be obtained by varying the reaction in the following way :

Alcohols may be obtained from aldehydes, ketones, and esters by methods which offer a close analogy to the zinc alkyl reactions.

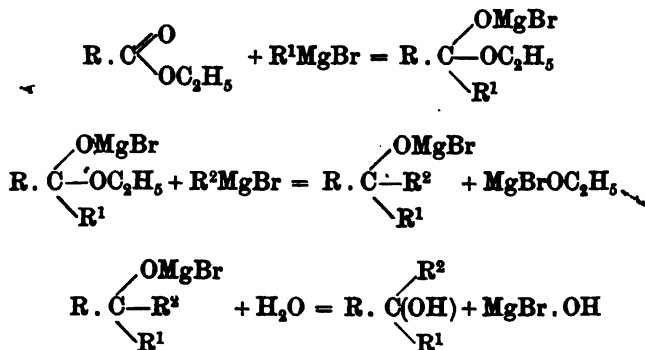
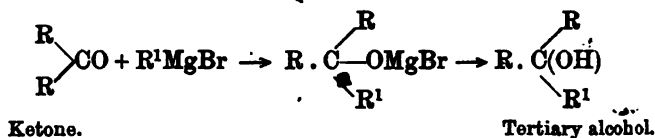


Aldehyde.

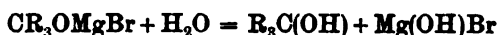
Secondary alcohol.

¹ Schmidt, Ahrens' *Vorträge*, 1905, 10, 68.

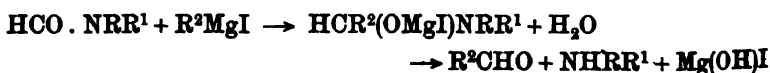
Primary alcohols can be obtained from formaldehyde or its polymeric form, trioxymethylene, in the same way.



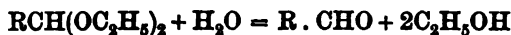
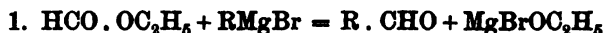
Carbonyl chloride also gives a tertiary alcohol.



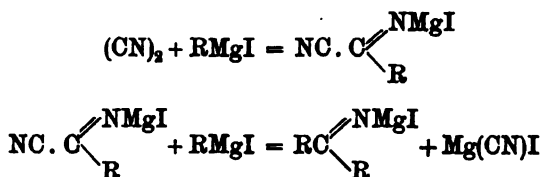
Aldehydes can be prepared from dimethylformamide,

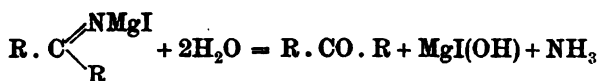


and also from formic ester and orthoformic ester, the product being decomposed with sulphuric acid.

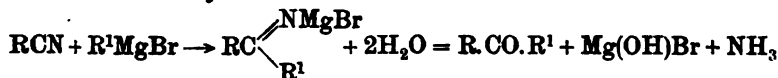


Ketones can be prepared from cyanogen, cyanides, and amides.

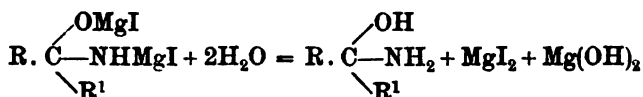
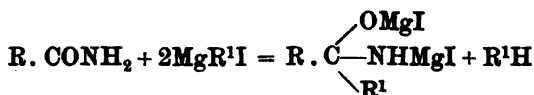




In the same way

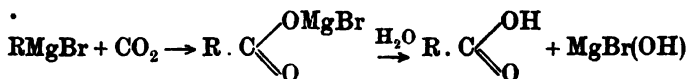


The action upon amides is represented as follows :

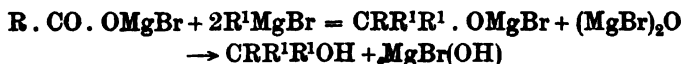


The last product loses ammonia and gives the ketone.

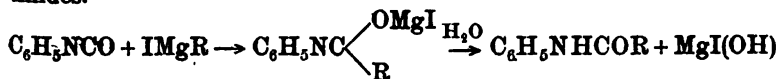
Acids are obtained by passing carbon dioxide into the ethereal solution of the magnesium alkyl compound and decomposing the product with water, sulphuric acid, or, if the sodium salt is required, with sodium hydroxide solution.



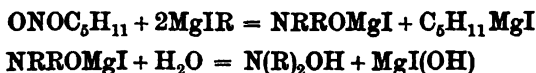
If the intermediate compound is further acted upon by two molecules of magnesium alkyl halide, and the product decomposed with water, a tertiary alcohol is formed.



Amides of the aromatic series may be obtained from aryl carbimides.



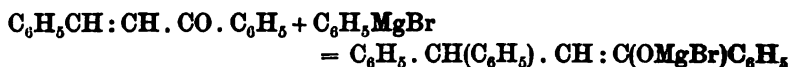
Hydroxylamine derivatives may be obtained from amyl nitrite as follows :



Additive Compounds¹ are also formed between magnesium alkyl

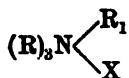
¹ Kohler, *Amer. Chem. J.*, 1906, 33, 153, 333; 34, 182.

halides and unsaturated ketones of the formula $R \cdot C : C \cdot CO \cdot C_6H_5$, thus:

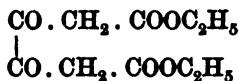


This does not exhaust the many changes which may be ^{sup}rought on the reaction, but the examples will serve to illustrate the general character of the process. It will be seen that, apart from the simplicity and convenience of the method, the magnesium alkyl compounds are much more reactive than the zinc alkyls, and their combination may be effected with nitrogen much in the same way as with oxygen, thereby increasing the range of their application.¹

It has been suggested by Tschelinzeff² that the ether which appears to form a compound with the magnesium alkyl halide acts catalytically at low temperatures, for he has found that by using an inert solvent, such as benzene, the formation of the organo-magnesium compound will be formed if mere traces of ether are added. He considers that the effect of the ether is to dissociate the alkyl halide by forming an oxonium compound and so facilitate union with the metal. Tertiary amines like dimethylaniline may replace ether as the catalyst, and their action is explained in a similar way by the disruption of the alkyl halide $R^1 X$ to form the quinquivalent compound.



Reformatsky's Reaction. A reaction which may be regarded as a modification of Frankland's and Grignard's was first suggested by Fittig and Daimler.³ They attempted to combine chloroacetic ester with oxalic ester in presence of zinc, in the expectation of obtaining a product similar to that of Frankland in which the acetic ester group would play the part of an alkyl radical. The reaction, however, gave instead ketipic (keto-adipic) ester.



Ketipic ester.

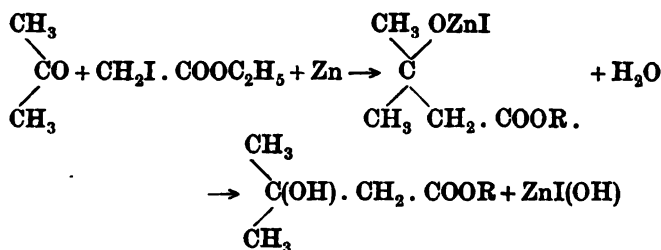
Reformatsky⁴ was afterwards more successful, and obtained from acetone, iodoacetic ester and zinc a β -hydroxy-isovaleric ester.

¹ A complete bibliography up to 1905 is given in the *Amer. Chem. J.*, 1905, 33, 318.

² *Ber.*, 1904, 37, 2084.

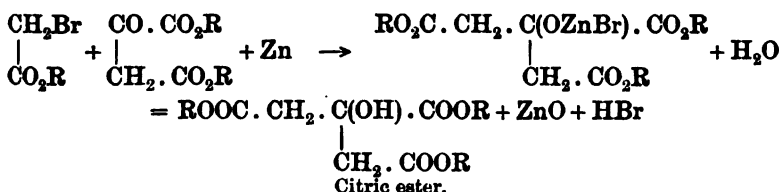
³ *Ber.*, 1887, 20, 202.

⁴ *Ber.*, 1887, 20, 1210; 1895, 28, 2468, 2838.

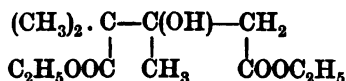


The reaction has since been used for the synthesis of citric acid by Lawrence,¹ *dl*-camphoronic acid by Perkin and Thorpe,² and for similar condensations.

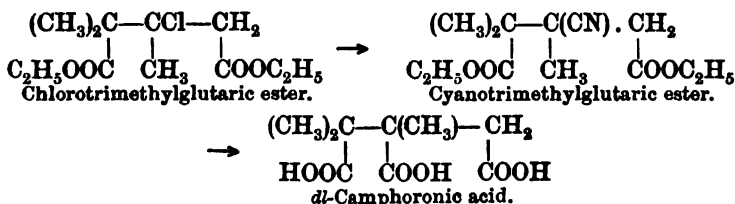
In the first case union is effected between bromacetic ester and oxalylacetic ester, and proceeds as follows:



In the second synthesis, α -bromoisobutyric ester and acetoacetic ester, or bromacetic ester and dimethylacetoacetic ester in presence of zinc were first combined, giving hydroxytrimethylglutaric ester.



The compound was then acted on with phosphorus pentachloride and converted into chlorotrimethylglutaric ester. On boiling with alcoholic potassium cyanide cyanotrimethylglutaric ester is formed, and finally, on hydrolysing with hydrochloric acid, *dl*-camphoronic acid.



Magnesium has been used in place of zinc in the above reaction.³

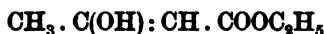
¹ *Trans. Chem. Soc.*, 1897, 71, 457.

² *Trans. Chem. Soc.*, 1897, 71, 1178.

³ Zelinsky and Gutt, *Ber.*, 1902, 35, 2140.

The Acetoacetic Ester Condensation. The discovery of acetoacetic ester carries us back to the year 1868, when Geuther,¹ who held the view that acetic acid contains two hydrogen atoms replaceable by metals, sought to replace the second hydrogen atom in ethyl acetate (since it could not be effected with sodium acetate) by means of metallic sodium.

He observed the evolution of hydrogen,² the formation of sodium ethoxide, and the production of a crystalline sodium compound of the formula $C_6H_5NaO_3$. From the sodium compound, by the addition of an acid, a liquid was isolated which, though neutral to litmus, formed salts with metallic bases. He found, moreover, that the sodium of the sodium compound reacts with alkyl iodides and forms a series of alkyl ethers. These facts led Geuther to name the new compound *ethyl diacetic acid*, and to represent it by the formula :



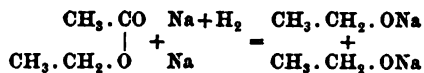
The formation of the sodium salt was represented by the equation :



Whilst this research was in progress Frankland and Duppa were studying the action of alkyl iodides on oxalic ester in presence of zinc. In extending their investigations to ethyl acetate, the zinc was replaced by the more energetic metal, sodium, and during the solution of the metal in the ester the evolution of hydrogen was observed. Without isolating the product they proceeded to heat up the solid mass with ethyl iodide. In this way various products were obtained and separated by fractional distillation. Among them four compounds boiling between 120° and 265° were isolated and characterized as follows : (1) *butyric ester*, (2) *diethylacetic ester*, (3) a compound identical with the ethyl ester of Geuther's ethyl diacetic acid, which, since it decomposed with alkalis into ethyl acetone, alcohol, and carbon dioxide, was termed *ethacetone carbonate of ethyl*, and (4) a final fraction which decomposed in the same manner into diethyl acetone, alcohol, and carbon dioxide, and received the name of *diethacetone carbonate of ethyl*. Frankland and Duppa explained the

¹ *Jahresb.*, 1868, 328.

² It was subsequently found that when ethyl acetate is pure little if any hydrogen is evolved, but according to Oppenheim and Precht (*Ber.*, 1877, 9, 320) it is used in conjunction with sodium to convert some of the acetic ester into sodium ethoxide.



formation of the first two compounds by supposing that ethyl acetate is converted by sodium into a mono- and di-sodium ethyl acetate,

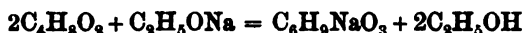


which with ethyl iodide yield ethyl- and diethyl-acetic ester. The formation of ethacetone and diethacetone carbonate of ethyl was explained by the union of a molecule of ethyl acetate with a molecule of mono- or di-sodium acetic ester formed by the action of sodium on acetic ester.



The action of ethyl iodide on the two sodium compounds would produce ethacetone and diethacetone carbonic esters. These views were generally accepted, and the name of Geuther's ethyl diacetic acid was subsequently changed to acetoacetic ester.

But in a subsequent paper¹ Geuther pointed out that he had failed to isolate either the mono- or di-sodium acetic ester; but had found that a considerable quantity of acetoacetic ester is formed by the action of sodium ethoxide on ethyl acetate, a reaction which he represented as follows:

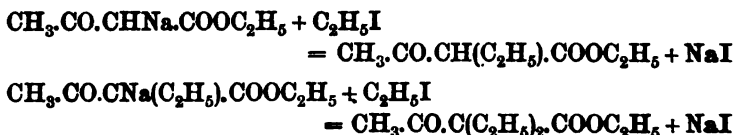


He observed at the same time that when the ethyl derivative of acetoacetic ester is heated with sodium ethoxide, ethyl butyrate is produced. It is therefore unnecessary to assume the formation of the monosodium compound of ethyl acetate, since the presence of sodium ethoxide alone will explain, in accordance with Geuther's original equation, the formation of both acetoacetic ester and ethyl butyrate. The production of diethylacetic ester and diethylacetoacetic ester (Frankland and Duppa's diethacetone carbonate of ethyl) still remained unexplained. In a paper published in 1877 by J. Wislicenus,² the whole subject was submitted to a critical re-examination with results which have proved of the highest importance to synthetic organic chemistry. Wislicenus showed that, although only one atom of hydrogen in acetoacetic ester can be replaced by sodium by the direct action of the metal, or of sodium ethoxide, an alkyl group having been introduced in place of this atom of sodium, the compound acquires the property of exchanging a second atom of hydrogen for sodium, which can be replaced by a second alkyl group.

¹ *Zeit. Chem.*, 1868, 652.

² *Annalen*, 1877, 186, 168.

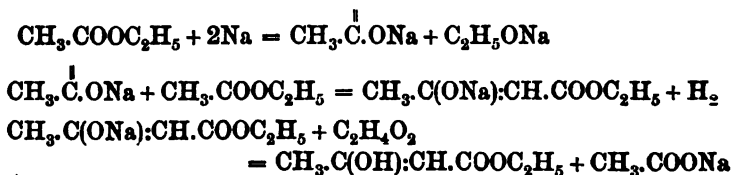
Wislicenus, adopting Frankland's formula, represented the changes as follows :



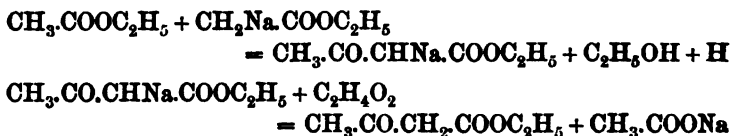
As the second product yields, with sodium ethoxide, diethylacetic ester, Frankland and Duppa's assumption of a disodium acetic ester proved as unnecessary as that of the monosodium compound.

But Wislicenus' inquiry was not limited to unravelling Frankland and Duppa's experiments. The knowledge of the numerous transformations which acetoacetic ester undergoes, the formation of mono- and di-alkyl derivatives, the conditions which determine the ketonic and acid hydrolysis, and the synthetic method for preparing acids and ketones by a combination of the two processes, are due to him and now belong to the most familiar synthetic reactions in organic chemistry. Although Wislicenus accepted Frankland's formula for acetoacetic ester in opposition to Geuther's, as the most simple explanation of its behaviour, he did not succeed in throwing any new light on the manner in which acetoacetic ester is produced.

Geuther,¹ who regarded both the sodium compound and the free ester as possessing the hydroxyl, or, as we now say, the enolic structure, explained the process in the following manner :



Frankland and Duppa², on the other hand, represented the reaction as due to the formation of a sodium compound of acetic ester, which unites with a second molecule of acetic ester.



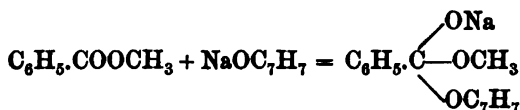
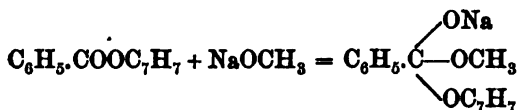
The controversy which the structure of acetoacetic ester aroused, and out of which the theory of tautomerism was ultimately evolved

¹ *Annalen*, 1888, 219, 123.

² *Phil. Trans.*, 1866, 156, 87; *Annalen*, 1866, 138, 204, 828.

(p. 174), diverted attention for a time from the mechanism of the reaction. In the meanwhile Frankland's ketonic structure for both the free ester and sodium compound, which expressed in a simple fashion the greater number of its transformations, was generally accepted.

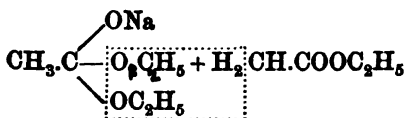
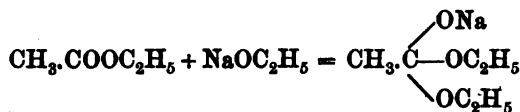
The first serious contribution to a theory of the acetoacetic ester synthesis is contained in a paper by Claisen¹ published in 1887, in which he shows that benzylbenzoate unites with sodium methylate and methyl benzoate with sodium benzylate to form the same additive compound.



Benzaldehyde also produces the same substance by the action of sodium methylate.



On the basis of this observation Claisen suggested that acetoacetic ester is produced in two stages. A molecule of sodium ethoxide unites with ethyl acetate and forms an additive compound, the latter combining with a second molecule of ethyl acetate to form sodium acetoacetic ester, with the elimination of two molecules of alcohol.

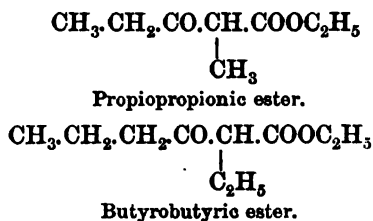


According to Claisen, therefore, the active agent in the process is not metallic sodium, but sodium ethoxide. This view received support from a variety of independent observations. Ladenburg in 1870 made the interesting discovery that ethyl acetate, carefully freed from alcohol by means of silicon chloride, is not attacked by sodium

¹ *Ber.*, 1887, 20, 646.

in the cold, and only very slowly on heating. It was also observed that, when ethyl acetate only contains a trace of alcohol, the action of sodium at the commencement is very slow, but increases in vigour as it proceeds, a fact which Claisen ascribed to the liberation of constantly increasing quantities of alcohol, as expressed in his equation. Moreover, Claisen's theory explained the enolic structure of the sodium compound, which was by this time generally recognized. But the most convincing proof of the active agency of sodium ethoxide was afforded by the large number of similar condensations effected between different esters or between esters and ketones either with alcohol-free sodium ethoxide, or, less frequently, with an alcoholic solution of sodium ethoxide in place of metallic sodium.

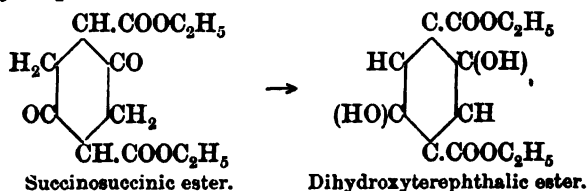
Some of these reactions will now be illustrated. It may be stated at the outset that the number of condensations effected with sodium ethoxide far exceeds that with metallic sodium. Acetic ester, however, gives a very much better yield with sodium than with sodium ethoxide, which even at 170° only produces about one-third of the theoretical amount. Sodium acts similarly with propionic and butyric ester, but with much diminished yields. The products of these two reactions have the structure :



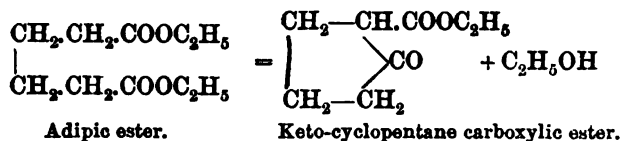
It follows, therefore, that the carbonyl group of the one ester molecule attaches itself to the α -carbon of the second, and that the reaction may be expressed in the following general form :



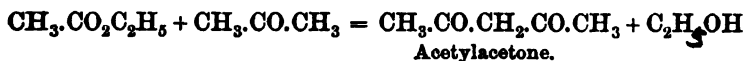
Succinic ester and sodium give the interesting cyclic compound succinosuccinic ester, which on oxidation is easily transformed into dihydroxyterephthalic ester :



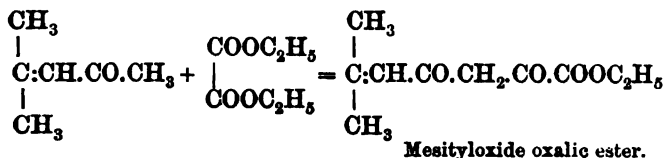
Cyclic compounds have also been produced by internal condensation, as for example by the action of sodium on adipic or pimelic esters.¹



Other examples of the use of metallic sodium are the following : the formation of acetylacetone from acetic ester and acetone.



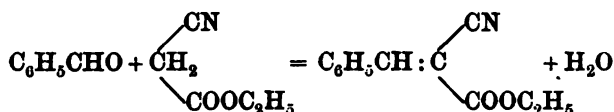
Mesityloxide oxalic ester is formed from mesityl oxide and oxalic ester,



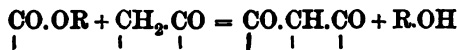
and cinnamic ester from benzaldehyde and acetic ester.



Sodium in minute quantities has also been used for effecting condensation between benzaldehyde and cyanacetic ester.



The above four examples exhibit considerable diversity both in the character of the substances used and in the nature of the product. The first two consist of a union between ester groups and the ketone group.



The last two, in which an aldehyde is used, belong to a rather different class of condensations, and are interesting in view of the fact that similar combinations can be effected by means of sodium hydroxide (p. 274) and by Perkin's reaction (p. 279).

Sodium ethoxide free from alcohol can be used for preparing a variety of products, in which two esters, an ester and a ketone, or an

¹ Dieckmann, *Ber.*, 1894, 27, 102.

ester and an aldehyde can be made to combine in much the same manner as with metallic sodium.

Benzoic and acetic ester yield benzoylacetetic ester.



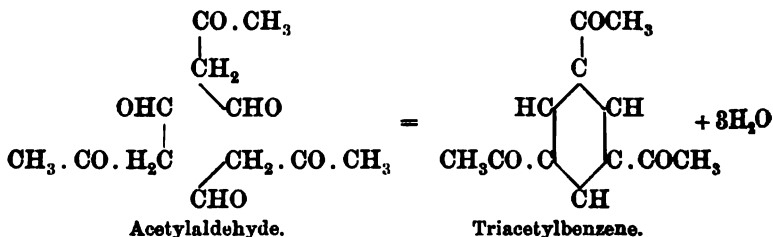
Benzoic ester and acetone form benzoylacetone.



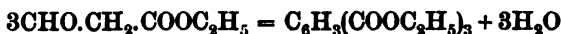
Benzoylacetophenone (dibenzoylmethane) is formed in a similar manner from benzoic ester and acetophenone. A variety of other compounds have been obtained by Claisen in a similar way.



W. Wislicenus has extended the method to the preparation of aldehyde esters and ketonic-dibasic esters by using formic ester on the one hand and oxalic ester on the other. Acetone and formic ester in presence of sodium ethoxide yield the sodium compound of acetylaldehyde, $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CHO}$, which on the addition of acetic acid almost immediately undergoes further condensation to triacetylbenzene.



Acetophenone and formic ester can be converted in the same way into tribenzoylbenzene. Formylacetic ester, which is obtained by condensing formic and acetic ester in presence of sodium, rapidly passes into trimesic ester at the ordinary temperature.¹



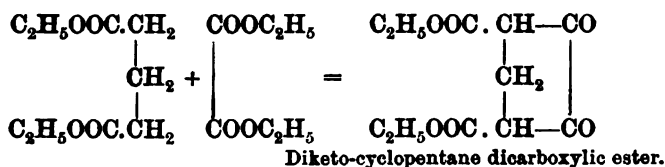
Formylphenylacetic ester, which is prepared with sodium ethoxide from formic and phenylacetic ester, yields two desamotropic forms (p. 189) but does not undergo further condensation.²

Oxalic ester has been a prolific source of new condensation products owing to the ease with which it combines, in consequence no doubt of its acidic character. In some cases an alcoholic solution of sodium ethoxide in place of the alcohol-free substance is

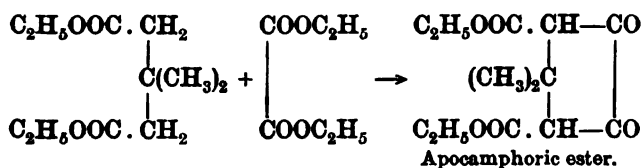
¹ Piutti *Ber.*, 1887, 20, 537.

² Wislicenus, *Ber.*, 1887, 20, 2930.

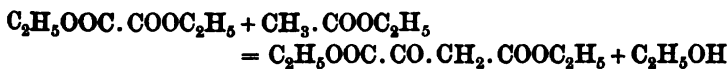
sufficient to induce condensation. A variety of ketonic cyclic compounds have been prepared. For example, by condensing glutaric and oxalic ester ¹ a derivative of cyclopentane is obtained :



and by combining $\beta\beta$ -dimethylglutaric ester with oxalic ester Komppa ² synthesized apocamphoric acid and later camphoric acid (p. 515).

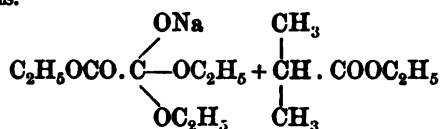


Acetic ester and oxalic ester yield oxaloacetic ester,



Oxalic ester also readily condenses with propionic and normal butyric ester but not with isobutyric ester.

In the latter observation Claisen saw a confirmation of his theory, to which we will now return ; for the structure of isobutyric ester does not admit of the removal of the two molecules of alcohol which the interaction of the additive compound of oxalic ester with sodium ethoxide demands.



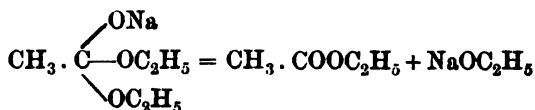
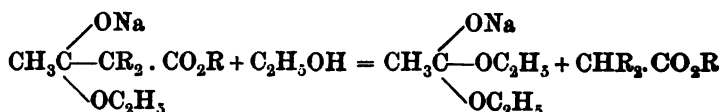
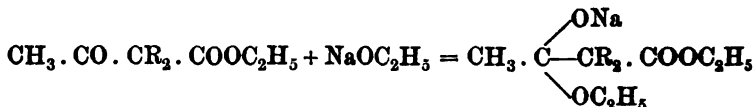
The fact has, however, received a much simpler interpretation from Dieckmann, ³ who has shown that the more acidic the β -ketonic ester, the less readily does it undergo acid hydrolysis with sodium ethoxide. Acetoacetic ester is very slowly hydrolysed at 180° with sodium ethoxide in alcoholic solution and is scarcely affected at the boiling temperature ; the monoalkyl esters change somewhat more readily, whilst the dialkyl esters are completely hydrolysed on warming the alcoholic solution containing a trace of sodium

¹ Dieckmann, *Ber.*, 1897, 30, 1470.

² *Ber.*, 1901, 34, 2472.

³ *Ber.*, 1900, 33, 2670.

ethoxide. The catalytic action of sodium ethoxide is explained by Dieckmann by supposing that a molecule of sodium ethoxide and then a molecule of alcohol are taken up by the ester and that the product then breaks up, regenerating sodium ethoxide:



It is clear, therefore, that the apparently passive character of isobutyric ester is due not so much to its structure as to the instability of the condensation product with oxalic ester. It seems to follow that the process depends in some measure on the acidic character of the final product, or, in other words, on the stability of the sodium compound of the ketonic ester. If this is so, it explains the remarkable differences which have been observed in the effect of the condensing agent, the velocity of the reaction, and the amount of the products.

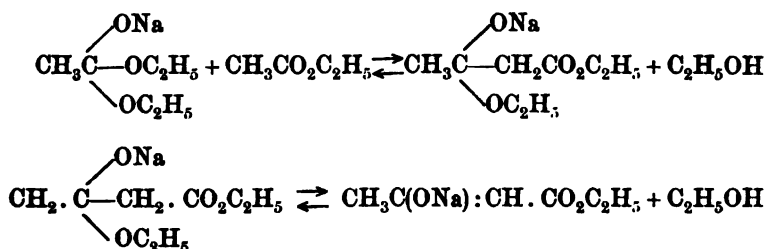
The sluggish action and unsatisfactory yield obtained with propionic and still more with butyric ester may be due to the more positive character of the product, whilst the readiness with which oxalic ester enters into reactions, especially with other acidic substances like acetophenone, may depend upon the enhanced stability of the sodium compound of the ketonic ester. We are, in fact, dealing with a wide range of reversible reactions in which the balance changes first to one side and then to the other.

We may inquire a little more fully into the mechanism of the changes just described. From what has been stated, one is almost forced to the conclusion that the use of sodium, of dry sodium ethoxide or its alcoholic solution, and latterly of sodamide, to which reference will be made presently (p. 272), only constitute modifications of the same fundamental process.

This in itself is a strong argument in favour of Claisen's theory. Claisen has, however, withdrawn somewhat from his original position.

In a recent paper¹ he reaffirms his view of the rôle which sodium ethoxide plays in forming an additive compound, but leaves undetermined the nature of the succeeding changes.

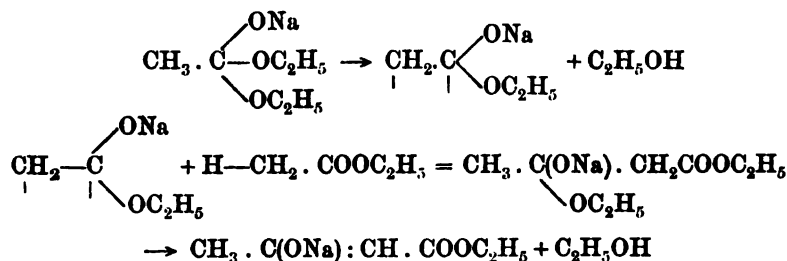
Dieckmann, by reversing the process by which he conceives hydrolysis with sodium ethoxide to be effected (p. 268), explains the acetoacetic ester synthesis by a series of reversible steps as follows :



This scheme at first sight does not appear to differ materially from Claisen's original conception ; but it implies that the condensation does not necessarily involve both steps, and that in some cases, especially where ring formation is involved, the removal of only one molecule of alcohol may occur and determine the final result.

Claisen's theory, even in its modified form, has not passed unchallenged. Nef² explains the acetoacetic ester and many other condensations as due to dissociation of hydrogen from carbon in the negative group of one molecule and the formation of an unsaturated group in the second, under the influence of the specific reagent.

In the present case Claisen's additive compound is supposed to lose alcohol and the unsaturated group in the nascent state to unite with the dissociated acetic ester molecule.



The dissociation is enhanced by the presence of negative atoms and groups, so that compounds containing carbonyl, cyanogen, and nitro-groups more easily undergo condensation. Malonic ester

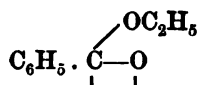
¹ *Ber.*, 1908, 36, 3674 ; 1905, 38, 709.

² *Annalen*, 1897, 298, 218.

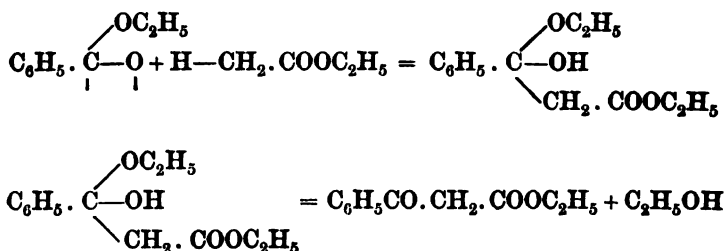
being more negative dissociates more easily into H and $\text{CH}(\text{COOR})_2$ than acetic ester into H and $\text{CH}_3 \cdot \text{COOR}$.

Those reagents which promote dissociation, acids, alkalis, metals, &c., assist condensation. The same principle is applied to other condensations.

The formation of benzoylacetic ester, which cannot be well explained, by supposing that hydrogen is dissociated from the nucleus in benzoic ester, is brought under a different scheme. Here the unsaturated group is



which unites with acetic ester as follows :



That the same kind of reaction should necessitate such different interpretations seems scarcely satisfactory.

Michael¹ has opposed Claisen's theory for many and various reasons, but chiefly on the ground that no additive compound such as Claisen describes has been isolated ; that there is no evidence that it exists ; that, moreover, the yield of acetoacetic ester is much diminished by substituting sodium ethoxide for sodium, whereas the reverse would be anticipated.

The formation of such an intermediate additive compound is also out of harmony with his 'neutralization law'. This law, which is based on energy changes, is developed at length in a series of papers, and though highly suggestive cannot be conveniently abridged.² Michael is perhaps more formidable as a critic than as a theorist, for his own explanation has a weak point, inasmuch as he draws a distinction between the mechanism of the change effected by sodium and that produced by sodium ethoxide. The explanation having reference to sodium is briefly as follows: The sodium, which is rich in positive,

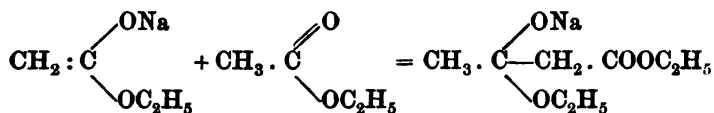
¹ *J. prakt. Chem.*, 1888 (2), 37, 507; *Ber.*, 1900, 33, 3781; 1905, 38, 1922.

² *J. prakt. Chem.*, 1888 (2), 37, 507; 1899 (2), 60, 286, 409.

potential energy, replaces hydrogen in acetic ester and gives rise to the compound $\text{CH}_2\text{Na} \cdot \text{COOC}_2\text{H}_5$, which isomerises at once to

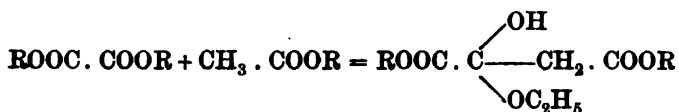


but the positive energy of the sodium is still unexhausted, and in the next phase the sodium acetic ester, which still possesses free positive energy, seizes on the carbonyl group of acetic ester, containing free negative energy, whereby the metal is so far neutralized that further condensation stops.

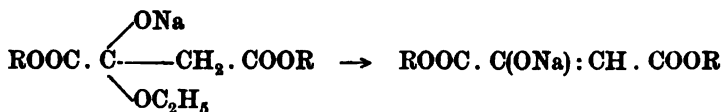


Finally, a molecule of alcohol is detached. The above change cannot be effected by sodium ethoxide as it possesses less free energy than metallic sodium.

It will be seen that so far as the acetoacetic ester synthesis is concerned there is no essential difference between the views of Michael and Nef. According to Michael, where sodium ethoxide is used, a process of polymerisation similar to the aldol condensation is induced (see p. 278). This condensation is brought about by the free energy of the carbonyl group in the one molecule and the mobility of the hydrogen atom, due to the proximity of a negative group, in the other molecule. Thus, the union of acetic and oxalic ester will be formulated as follows:



The product then interacts with sodium ethoxide and a molecule of alcohol is finally detached.



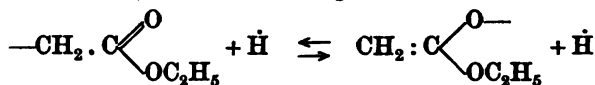
In the acetoacetic ester synthesis the sodium compound is formed previous to condensation, in the oxaloacetic ester it takes place after condensation.

A very ingenious and suggestive explanation of this and other condensations has been advanced by Lapworth.¹ Lapworth supposes

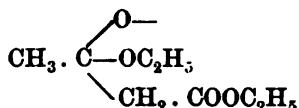
¹ *Trans. Chem. Soc.*, 1901, 79, 1269; 1902, 81, 1512; *Proc. Chem. Soc.*, 1903, 19, 190.

that the substance undergoes ionisation, forming an equilibrium mixture of ions (see p. 206).

Acetic ester will yield the following ions:



The presence of a base, by diminishing the concentration of the hydrogen ions, will increase that of the negative ions and accelerate the change. The first represents the negative ion of an organo-metallic compound and, being a weak ion, capable, by reason of its electro-affinity, of uniting with a neutral component,¹ i.e. a molecule of acetic ester, forming a new complex negative ion thus:



The process may be compared with that by which the alkyl group of a magnesium alkyl halide attaches itself to the carbon of a carbonyl group. The process being reversible, as Dieckman has shown (p. 267), the ion may lose its neutral component and break up into two molecules of acetic ester, or it may form a neutral substance with a positive ion, such as sodium, or it may lose the negative ion $-\text{OC}_2\text{H}_5$, in the form of alcohol, and form acetoacetic ester.

Before concluding the subject of the acetoacetic ester synthesis reference should be made to the introduction by Claisen of sodamide as a condensing agent.² In the majority of cases its action is quieter and more regular than either sodium or sodium ethoxide. It can be used in the synthesis of 1·3-diketones and for alkylating ketones. Acetophenone and ethyl iodide in presence of sodamide give ethyl-acetophenone. By the action of ethyl chloracetate on ketones, glycidic esters are formed. The latter reaction is explained by Claisen as proceeding in three phases. In the first an additive compound with sodamide is formed, which undergoes condensation with the ethyl chloracetate and is followed by the removal of sodium chloride.

1. $\text{C}_6\text{H}_5 \cdot \text{C}(\text{CH}_3)(\text{ONa}) \cdot \text{NH}_2$
2. $\text{C}_6\text{H}_5 \cdot \text{C}(\text{CH}_3)(\text{ONa})\text{CHCl} \cdot \text{COOC}_2\text{H}_5$
3. $\text{C}_6\text{H}_5 \cdot \text{C}(\text{CH}_3)\text{CH} \cdot \text{COOC}_2\text{H}_5$

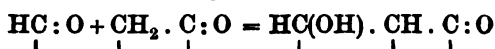


¹ See Abegg and Bodländer, *Zeit. anorg. Chem.*, 1899, 20, 475.

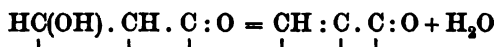
² *Ber.*, 1905, 38, 693.

The use of an aldehyde as one of the participating members in a condensation introduces a whole series of closely related reactions, among which are included the aldol condensation, Claisen's reaction, the benzoin condensation and Perkin's synthesis. These reactions can only be treated in a very general way.

The Aldol Condensation. This condensation, which was discovered by Wurtz,¹ occurs between aldehydes and ketones, and may be expressed by the following general scheme:



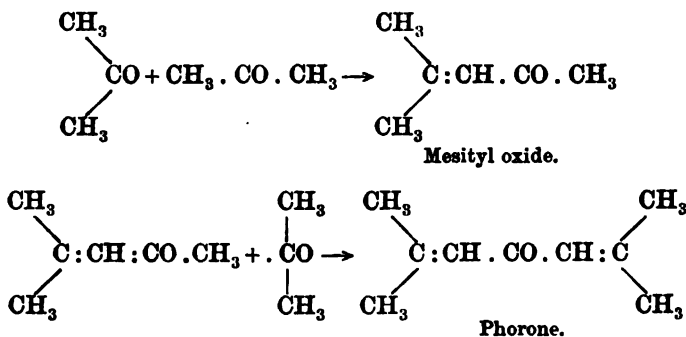
A second phase in the process results in the elimination of water and the production of an unsaturated compound.



The first is the aldol, the second the crotonaldehyde condensation. Sometimes the first phase is lost and only the second becomes manifest.

The usual reagents which effect the condensation are hydrochloric acid, potassium carbonate or caustic soda solution, and, less frequently, sulphuric acid, acetic acid, acetic anhydride, and zinc chloride.

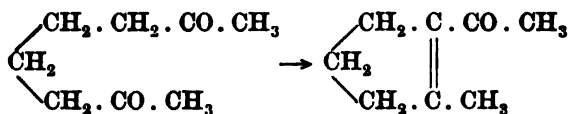
The type of all these condensations is the formation of aldol (hydroxybutylaldehyde) and crotonic aldehyde from acetaldehyde. The first reaction occurs in presence of hydrogen chloride or potassium carbonate, and the second, either by the action of heat on the aldol, or by the direct action of zinc chloride on acetaldehyde. The production of mesityl oxide and phorone by passing hydrogen chloride into acetone² is another example of the crotonaldehyde condensation.



¹ *Jahresb.*, 1872, 449.

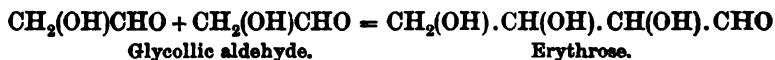
² Baeyer, *Annalen*, 1866, 140, 297.

The reaction has also been used for preparing unsaturated cyclic compounds. Diacetylbutane and strong sulphuric acid yield methyl-dehydrocyclopentene methyl ketone.¹

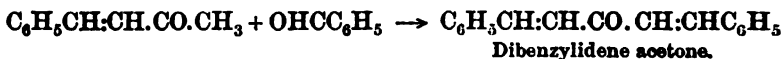
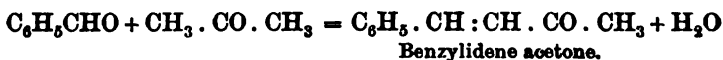


Diacetylpentane gives in the same way methyltetrahydrobenzene methyl ketone.²

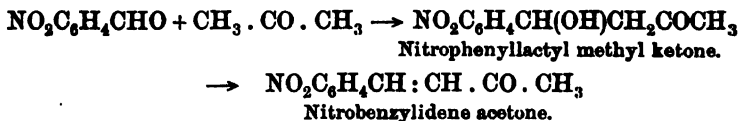
Claisen's Reaction. A special interest attaches to the use of dilute sodium hydroxide solution as condensing agent, which was first employed by Schmidt³ and afterwards studied by Claisen.⁴ Condensations between aldehydes and a variety of aldehydes and ketones have been effected by this reagent. The synthesis of erythrose from glycollic aldehyde (p. 299) and fructose from glycerose are examples of this process (p. 311).



In many cases the aldol phase is lost, and only the second phase appears. Claisen found that benzaldehyde and acetone in presence of sodium hydroxide solution (10 per cent.) yield benzylidene- and dibenzylidene-acetone.



With *o*-nitrobenzaldehyde and acetone Baeyer and Drewsen⁵ succeeded in arresting the action at the first stage and obtained the nitrophenyllactyl methyl ketone, which by boiling with acetic anhydride is converted into the unsaturated compound.



In this condensation an excess of alkali is to be avoided, otherwise indigo is formed.

¹ Marshall and Perkin, *Trans. Chem. Soc.*, 1890, 57, 241.

² Kipping and Perkin, *Trans. Chem. Soc.*, 1890, 57, 14.

³ *Ber.*, 1880, 13, 2842.

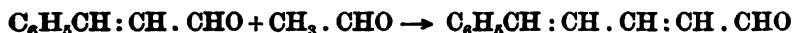
⁴ *Ber.*, 1881, 14, 2471.

⁵ *Ber.*, 1882, 15, 2857.

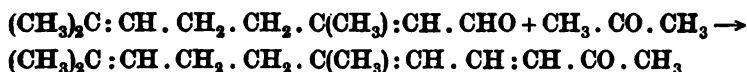
If the new compound obtained by means of this reaction is an aldehyde like cinnamic aldehyde (which is formed from benzaldehyde and acetaldehyde) the process of condensation may be repeated.



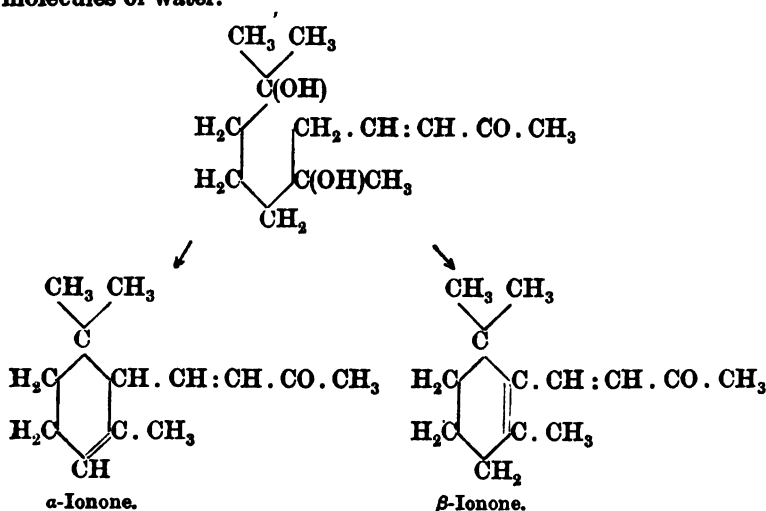
As Einhorn and Diehl¹ have shown, cinnamic aldehyde may undergo a second condensation with another molecule of acetaldehyde or acetone.



This method of condensation has received an interesting technical application in the preparation of *ionone*—a substitute for essence of violets, the sweet-smelling principle of which it closely resembles both in structure and perfume. Ionone was prepared by Tiemann and Krüger² from citral, an aldehyde contained in citron and lemon grass oil (p. 527). Citral and acetone condense in presence of baryta solution to form *pseudoionone*, which is converted in turn into a mixture of α - and β -ionone on boiling with sulphuric acid.



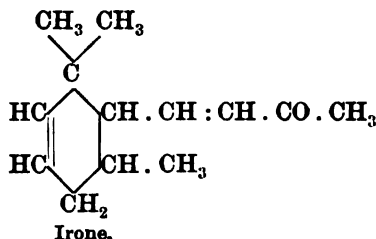
The conversion of pseudoionone into α - and β -ionone may be supposed to take place by the addition and subsequent removal of two molecules of water.



¹ Ber., 1885, 18, 2820.

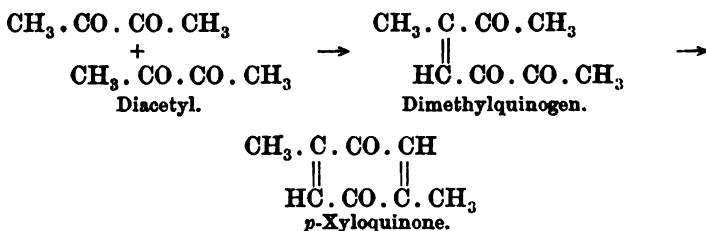
² Ber., 1898, 31, 808.

Irone, the perfume itself, is represented by the formula :¹

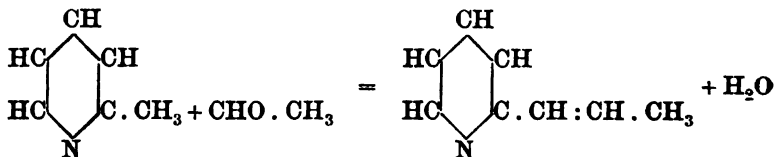


Like the aldehydes, diketones may undergo condensation with other ketones, and Japp² and others have succeeded in forming products by combining benzil and phenanthraquinone with acetone, &c. An interesting application of the same reaction is due to von Pechmann,³ who prepared quinones of the benzene series by a similar process.

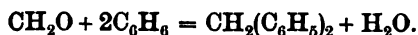
Thus, diacetyl and sodium hydroxide gave first the intermediate product *dimethylquinogen* and, by internal condensation, *p-xyloquinone*.



Acetyl propionyl forms in the same way duroquinone. To the same category of reactions belong the condensation of α -methyl pyridine and α -methyl quinoline with aldehydes and ketones (p. 567).



Many aliphatic and aromatic aldehydes also undergo condensation with aromatic compounds in which the carbon of the nucleus attaches itself to the carbon of the aldehyde group. In presence of strong sulphuric acid, formaldehyde unites with benzene to form diphenylmethane.

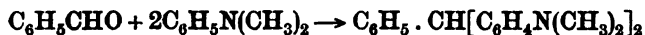


¹ Ber., 1898, 26, 2675.

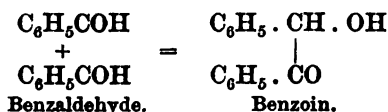
² Ber., 1888, 16, 275, 282.

³ Ber., 1888, 21, 1417.

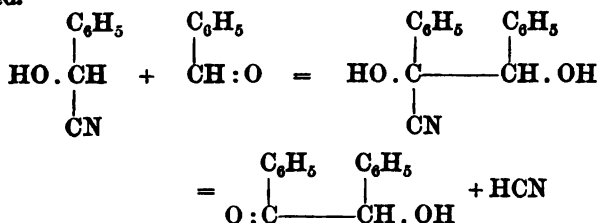
The formation of leucobenzaldehyde green is another example of the same process.



Benzoin Condensation. The action of potassium cyanide on aromatic aldehydes is a peculiar one, and may be represented by the oldest example—the formation of benzoin from benzaldehyde and alcoholic potassium cyanide—which was first studied by Liebig and Wöhler.¹



The reaction bears a close resemblance to the aldol condensation. The specific action of the cyanide, which differs fundamentally from that of the caustic alkalis or sodium ethoxide (which produce benzyl benzoate or a mixture of benzyl alcohol and benzoic acid), has received various explanations,² the most plausible of which is that of Lapworth.³ Lapworth suggests that the benzaldehyde forms a cyanhydrin with potassium cyanide, which then condenses with another molecule of benzaldehyde, hydrogen cyanide being finally eliminated.



Pinacone Condensation. A reaction not unlike that which produces aldol and benzoin, and which was first observed by Fittig,⁴ is brought about by the action of neutral, alkaline, and occasionally acid reducing agents on aldehydes and ketones. In addition to primary and secondary alcohols, this reaction gives rise to substances known as *pinacones*. In this reaction the molecules of the original compound become linked by the aldehyde or ketone carbon atom; at the same time two atoms of hydrogen are taken up. The compounds

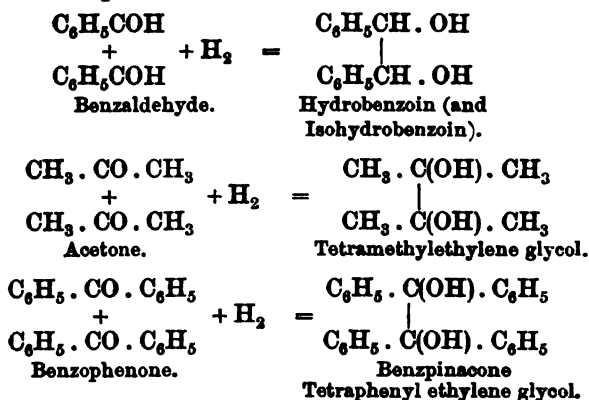
¹ *Annalen*, 1832, 3, 276.

² Knoevenagel, *Ber.*, 1888, 21, 1846; Nef, *Annalen*, 1897, 298, 312.

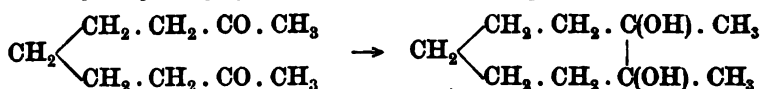
³ *Trans.*, 1903, 83, 995.

⁴ *Annalen*, 1858, 110, 26; 1859, 114, 54. The name pinacone has reference to the tabular form of the crystals obtained from acetone (*pinax* = table).

are in fact secondary or tertiary glycols. The following examples will illustrate the process :

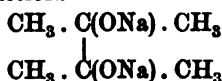


The first of the above reactions occurs only with aromatic aldehydes and a few of the higher aliphatic aldehydes, the two latter are alike shared by aliphatic and by aromatic ketones. The reaction has been used for inner condensation, as, for example, in the preparation of dimethyldihydroxy-cycloheptane from diacetylpentane.¹



The reduction is usually effected by sodium amalgam, the aluminium-mercury couple, zinc and acetic acid or zinc and hydrochloric acid.

No very clear explanation of the mechanism of the process is yet forthcoming. The action of sodium on aldehydes and ketones has been studied by Fittig, Beckmann and Paul, and also by Freer, and may possibly throw some light on the subject. Kane, early in the nineteenth century, found that potassium liberates hydrogen from acetone and forms a compound $\text{C}_3\text{H}_5\text{OK}$, and more recently Freer² stated that he had obtained a similar compound by the action of sodium, to which he assigned the formula $\text{CH}_3 \cdot \text{C(ONa)} : \text{CH}_3$. Fittig's³ observation that sodium acts upon acetone with the production of a sodium compound of pinacone receives a ready interpretation if we assume that two molecules of a nascent sodium acetone become linked in process of reduction.

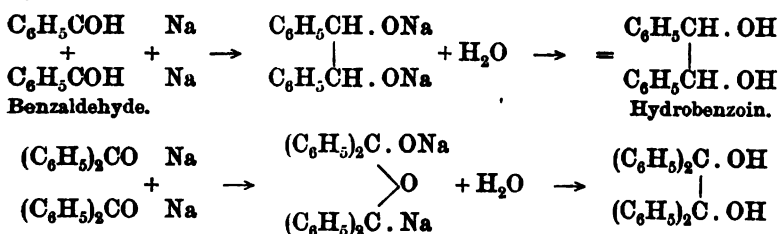


¹ Kipping and Perkin, *Trans. Chem. Soc.*, 1891, 59, 214.

² *Amer. Chem. J.*, 1898, 15, 582; see also Taylor, *Trans. Chem. Soc.*, 1906, 89, 1253.

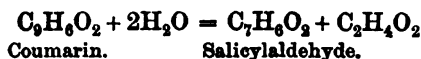
³ *Annalen*, 1859, 110, 25; 1860, 114, 54.

Beckmann and Paul¹ have shown in the same way that benzaldehyde and benzophenone form sodium compounds which are decomposed by water.

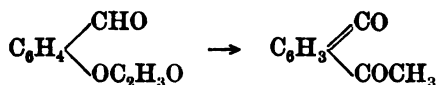


In the latter case benzhydrol is also formed.

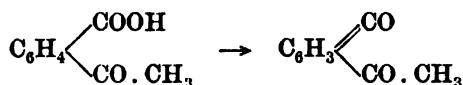
Perkin's Reaction. The history of this interesting reaction dates from Perkin's synthesis of coumarin in the year 1868.² Coumarin, the sweet-smelling principle of woodruff and hay, was found to decompose, on fusion with potassium hydroxide, into salicylic aldehyde and acetic acid,



from which the natural conclusion was drawn that coumarin was the anhydride of acetylsalicylaldehyde.



By heating sodium salicylaldehyde with acetic anhydride, coumarin was, in fact, obtained. The evidence seemed conclusive until it was discovered that acetylsalicylaldehyde is unchanged by acetic anhydride, although, with the addition of fused sodium acetate, coumarin is readily produced. The formula assigned by Perkin, which represented coumarin as a derivative of acetylsalicylaldehyde, was disputed by Fittig, who could not reconcile it with the constitution of coumaric acid, of which it is the anhydride; for coumaric acid must then form coumarin by the removal of hydrogen from the benzene nucleus, a process which seemed difficult to reconcile with the properties of the compound.



Fittig preferred to base his view of its constitution on a reaction dis-

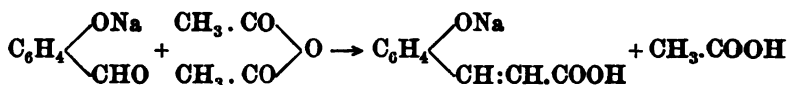
¹ *Annalen*, 1892, 266, 1.

² *Trans. Chem. Soc.*, 1868, 21, 58.

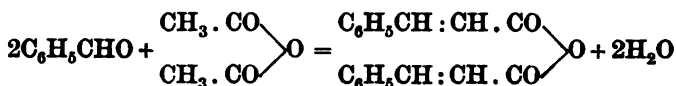
covered by Bertagnini¹ for the preparation of cinnamic acid, which consisted in heating benzaldehyde and acetyl chloride.



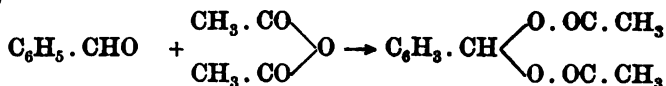
The formation of coumarin might be explained in an analogous fashion.



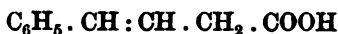
The formula for coumarin as the inner anhydride of *o*-hydroxycinnamic acid is now universally accepted.² In 1877³ Perkin published a new method for preparing cinnamic acid and analogous compounds by means of a reaction of very general application which now bears his name. It consists in heating a fatty or aromatic aldehyde and the anhydride of a fatty acid together with its sodium salt to 180° for several hours. The formation of cinnamic acid from benzaldehyde, acetic anhydride and sodium acetate was explained by Perkin on the assumption that the anhydride acted upon the aldehyde in the following manner:



The view was, however, opposed to the observation of Geuther and Hübner, who found that benzaldehyde and acetic anhydride yield benzylidene acetate.



To determine the point, Perkin heated benzaldehyde and acetic anhydride with sodium propionate and obtained cinnamic acid, whereas with propionic anhydride and sodium propionate, phenyl crotonic acid was formed. Perkin assigned to phenyl crotonic acid the formula:

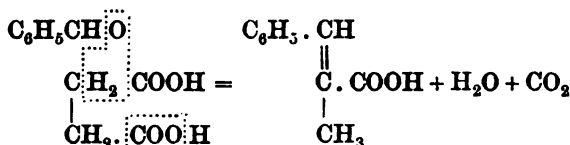


¹ *Annalen*, 1856, 100, 126.

² According to Michael (*J. prakt. Chem.*, 1899, 60, 368) Strecker was the first to propose this formula in his *Lehrbuch*.

³ *Trans. Chem. Soc.*, 1877, 31, 389.

By the interaction of benzaldehyde, succinic anhydride and sodium succinate, a second or isophenylcrotonic acid was subsequently prepared by Perkin, the formation of which received the following interpretation:



Fittig,¹ who had been engaged in a careful study of the unsaturated acids, was unable to reconcile the properties of the two phenylcrotonic acids with the respective formulae assigned by Perkin. The $\alpha\beta$ unsaturated acids possess the following properties in common: the additive compounds with hydrobromic acid, when heated in aqueous solution, either lose hydrogen bromide and pass back into the original compound or the bromine atom is replaced by hydroxyl, whilst in alkaline solution, carbon dioxide and hydrogen bromide are removed, and an unsaturated hydrocarbon results. β -bromophenylpropionic acid reacts in the following way:

1. $\text{C}_6\text{H}_5\text{CHBr} \cdot \text{CH}_2 \cdot \text{COOH} = \text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH} \cdot \text{COOH} + \text{HBr}$
2. $\text{C}_6\text{H}_5\text{CHBr} \cdot \text{CH}_2 \cdot \text{COOH} + \text{H}_2\text{O}$
 $\quad \quad \quad = \text{C}_6\text{H}_5\text{CH}(\text{OH}) \cdot \text{CH}_2 \cdot \text{COOH} + \text{HBr}$
3. $\text{C}_6\text{H}_5\text{CHBr} \cdot \text{CH}_2 \cdot \text{COONa} = \text{C}_6\text{H}_5\text{CH} : \text{CH}_2 + \text{NaBr} + \text{CO}_2$

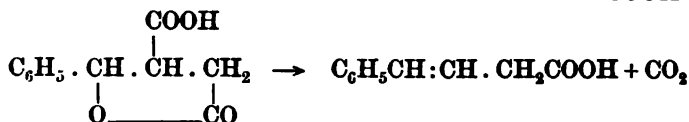
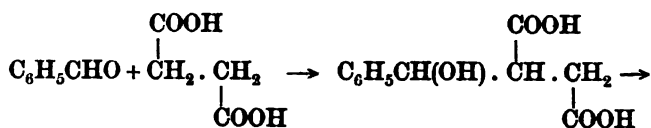
It was the first and not the second phenylcrotonic acid which behaved in this way and gave with sodium hydroxide solution the unsaturated hydrocarbon, methyl styrene $\text{C}_6\text{H}_5\text{CH} : \text{CCH}_3$. The two formulae must consequently be reversed. It follows, therefore, that in the reaction between benzaldehyde and propionic acid, it is the α -carbon of the acid which attaches itself to the carbon of the aldehyde group.²

In order to follow the phases of the second reaction Fittig and Jayne³ repeated Perkin's experiment with benzaldehyde, succinic anhydride and sodium succinate, but at a temperature of 100° instead of 180° , with the following interesting results: no carbon dioxide was evolved, but phenyl paraconic lactone was formed, which, on heating, evolved carbon dioxide and yielded isophenylcrotonic acid. Fittig explained the changes as follows:

¹ *Ber.*, 1894, 27, 2658.

² This view had already found expression in Markownikoff's law, *Annalen*, 1868, 146, 848, and had been further insisted on by Michael (*Ber.*, 1878, 11, 1015).

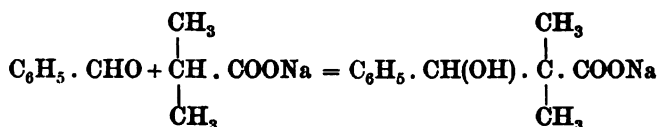
³ *Annalen*, 1882, 216, 97.



Phenylparaconic lactone.

Isophenylcrotonic acid.

The production of a hydroxy compound, which, as in the aldol condensation, Fittig assumed to represent the first phase of the process, was rendered still more probable by the formation of phenylhydroxypivalic acid from benzaldehyde and sodium isobutyrate in presence of acetic anhydride.¹

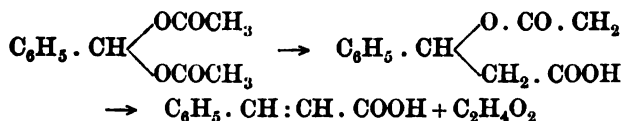


Phenylhydroxypivalic acid.

Fittig found, moreover, that in the preparation of phenyl paraconic lactone at the lower temperature, acetic anhydride may replace with advantage succinic anhydride, and this led him to infer that it is the aldehyde and the sodium salt which interact, and not, as Perkin had assumed, the aldehyde and anhydride. By conducting the process at 100° he, in fact, obtained from benzaldehyde, sodium propionate and acetic anhydride, phenylcrotonic acid, and from sodium butyrate and acetic anhydride, phenylangelic acid. The fact that Perkin had obtained cinnamic acid from benzaldehyde, acetic anhydride and sodium propionate now received a simple explanation, for if the reaction is conducted at 100°, the sodium salt of the acid reacts, whereas at 180° double decomposition will occur between the acetic anhydride and sodium propionate or sodium butyrate, yielding sodium acetate and propionic anhydride or butyric anhydride. The sodium salt then produces, with benzaldehyde, cinnamic acid. Fittig's view received apparent confirmation from the experiments of Stuart,² who prepared analogous compounds with malonic and isosuccinic acids, both of which are incapable of forming anhydrides. Fittig then drew the following conclusions: Perkin's reaction occurs between the aldehyde and the sodium salt of the acid in two stages; in the first a hydroxy compound is formed, condensation taking place between

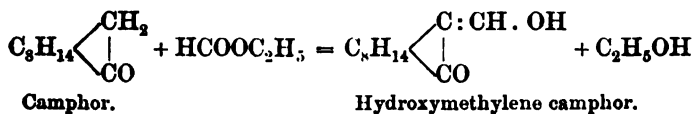
¹ *Annalen*, 1882, 216, 115.² *Ber.*, 1888, 16, 1486.

the aldehyde and α -carbon of the acid; in the second, water is eliminated; in the case of polybasic acids a lactone may be formed from which water and carbon dioxide can be removed on heating. In spite of apparently convincing proofs, Perkin¹ did not relinquish his original view that the interaction takes place between the anhydride and the aldehyde, a view which is also shared by Michael. Perkin pointed out, for example, that the formation of phenylangelic acid on heating a mixture of benzaldehyde, sodium butyrate and acetic anhydride to 100° does not prove that combination occurs between the aldehyde and the sodium salt; for, in the first place, cinnamic acid cannot be formed under any circumstances at this low temperature, and secondly, the sodium salt and acetic anhydride react readily at 100° to form sodium acetate and butyric anhydride, and the same is true of the salts of other higher fatty acids.² Perkin suggested that in the preparation of cinnamic acid, the benzylidene diacetate which is produced by the interaction of benzaldehyde and acetic anhydride, and which is known to decompose into cinnamic acid, may undergo isomeric change and then lose a molecule of acetic acid.



Perkin's theory of the process bears a strong resemblance to that recently suggested by Claisen³ to explain the acetoacetic ester synthesis. These conflicting results are difficult to adjust, and the question of the course of the reaction must be left for the present undecided.

Condensations with 1.3-Diketones, Claisen's Method. In studying the action of formic ester on camphor in presence of sodium alcoholate, Claisen⁴ obtained *hydroxymethylene camphor*.



The condensation product possesses strongly acid properties and forms salts and esters after the manner of acids.



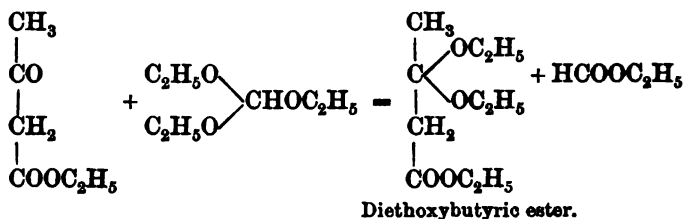
¹ *Trans. Chem. Soc.*, 1886, 47, 317.

² Michael, *J. prakt. Chem.*, 1899, 60, 364.

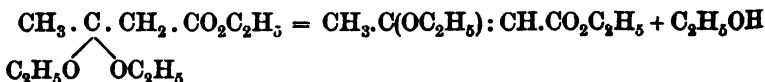
³ *Ber.*, 1903, 36, 3674; 1905, 38, 709.

⁴ *Annalen*, 1894, 281, 306.

With acetic anhydride and benzoyl chloride it yields an acetyl and benzoyl derivative. But the most significant reactions occur with phosphorus trichloride and the bases, ammonia, aniline, and methyl-aniline. In the first case the hydroxyl is replaced by chlorine, in the second, by the radicals of the three basic groups forming amides. It follows, therefore, that the new carbon group contains hydroxyl. and since it can only be represented by the unsaturated group $=CH(OH)$, the term *hydroxymethylene* has been given to it. The results of this research led to the discovery of other hydroxymethylene compounds possessing still more marked acid properties. By the action of acid chlorides on acetoacetic ester or its metallic compounds the acyl group may replace hydrogen either in the methylene group of the keto form, or in the hydroxyl group of the enol form.¹ Since no acid chloride of formic acid exists, the simplest of the acyl derivatives, namely, formylacetoacetic ester, could not be obtained in this way. Formic ester, which might be employed as a substitute for the acyl chloride, does not condense with acetoacetic ester in presence of sodium ethoxide, owing no doubt to the formation of the sodium compound of acetoacetic ester, which would inhibit any further action. This suggested the use of orthoformic ester, but this substance in presence of acetyl chloride condenses in the following unexpected fashion, giving diethoxybutyric ester.²



The latter on distillation loses a molecule of alcohol and forms ethoxycrotonic ester, the isomer of ethylacetoacetic ester.

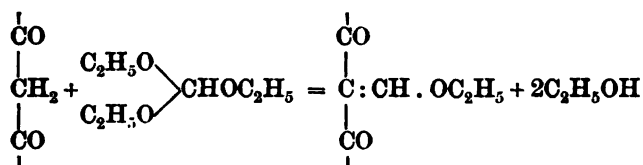


If, however, acetic anhydride is employed as condensing agent, the following reaction occurs, which is shared by other 1.3-diketones such as malonic ester, acetylacetone, &c.³

¹ The replacement of the radical in the hydroxyl of the enol form is best accomplished by means of the acyl or alkyl halide in presence of pyridine.

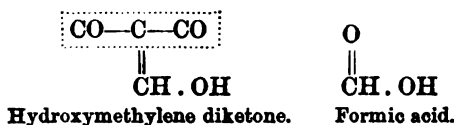
² *Ber.*, 1898, 26, 2729.

³ *Annalen*, 1897, 297, 1.

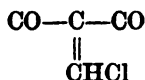


These substances represent esters of strong monobasic acids, for they are hydrolysed either by water or alkalis yielding the free acid or its salt, and are converted into amides by ammonia or amines. The strength of the acids, as determined from their electrical conductivities, is of the order of acetic acid. Claisen concludes that the group

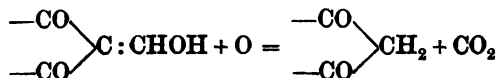
$\text{CO}-\overset{|}{\text{C}}-\overset{|}{\text{CO}}$ which is present in these substances may play the part of the $=\text{O}$ atom in a carboxylic acid, a view which is readily understood by a comparison of the two atomic groupings, the dotted line enclosing the equivalent of the doubly linked oxygen in formic acid.



The presence of the hydroxymethylene group in these compounds is proved, as in hydroxymethylene camphor, by the action of phosphorous chloride, which removes hydroxyl, giving the acid chloride.



On heating the latter with the sodium salt of the acid, a compound having all the characteristics of an anhydride is produced. The free acids rapidly absorb oxygen and, on warming, evolve carbon dioxide, when the original diketone is regenerated.

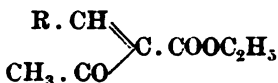


The compounds undergo various other interesting changes, for an account of which the original paper must be consulted.

Knoevenagel's Reaction. Among the earlier attempts to bring about condensation of aldehydes and ketones with 1.3-diketones and ketonic esters is that of Claisen,¹ who, by the use of hydrogen chloride,

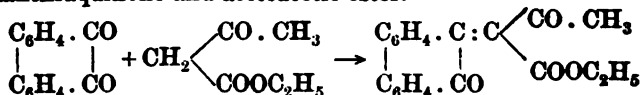
¹ *Annalen*, 1888, 218, 172.

succeeded in obtaining condensation products with acetaldehyde, benzaldehyde, and acetoacetic ester of the formula:

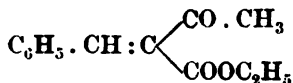


Much more effective reagents for this purpose are ammonia and the primary and secondary bases.

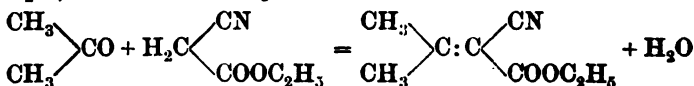
Japp and Streatfeild¹ were the first to employ ammonia to condense phenanthraquinone and acetoacetic ester.



In 1898 Knoevenagel² carried out a much more complete investigation, in which not only ammonia, but diethylamine, piperidine, and aniline were used with success. Thus, benzaldehyde in presence of small quantities of diethylamine condenses with acetoacetic ester, when cooled in a freezing mixture, forming benzylidene acetoacetic ester, that is, the compound which Claisen obtained with hydrogen chloride.



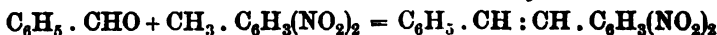
This example may serve as the type of a very general process in which, on the one hand, aldehydes and ketones may be used, on the other hand a variety of 1.3-diketones and ketonic esters, like malonic ester, benzoylpyruvic ester, benzoylactic ester, acetonedicarboxylic ester, acetylacetone, benzoylacetone, and cyanacetic ester. Acetone, for example, condenses with cyanacetic ester.



Also, aliphatic and aromatic nitro-compounds may replace the 1.3-diketone,



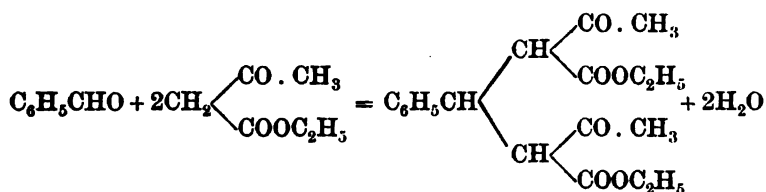
and 2.4-dinitrotoluene condenses with benzaldehyde.



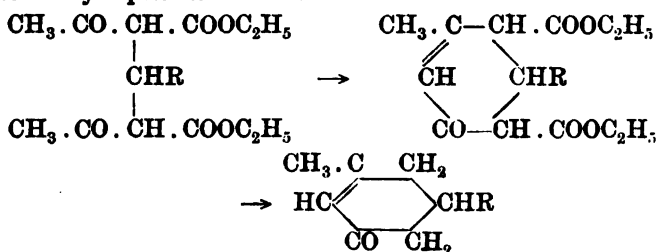
In some cases a double molecule of the 1.3-diketone condenses with the aldehyde if the process is conducted under modified conditions. Thus, benzaldehyde and acetoacetic ester condense in presence of diethylamine, if the reaction proceeds at the ordinary temperature, to form benzylidene diacetoacetic ester.

¹ *Trans. Chem. Soc.*, 1883, 43, 27.

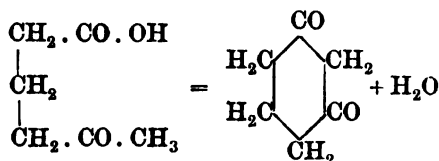
² *Annalen*, 1894, 281, 25; *Ber.*, 1904, 37, 4461.



Compounds of this character, which may be described as 1.5-diketones, are capable of internal condensation in presence of alkalis or hydrochloric acid, and a variety of cyclic compounds have been built up in this manner, of which the following is an example.¹ Alkylidene diacetoacetic ester undergoes inner condensation with alcoholic potassium hydroxide, and on hydrolysis loses carbon dioxide and yields the cyclopentenone derivative.



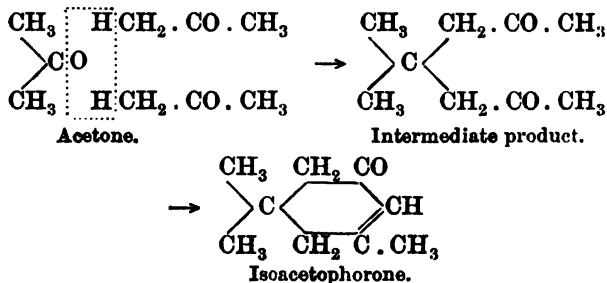
Analogous reactions to the above are the inner condensation of 1.5-ketonic acids and ketones,² such as the synthesis of dihydroresorcinol from γ -acetyl butyric acid,



γ -acetyl butyric acid.

Dihydroresorcinol.

and the formation of isoacetophorone from acetone and lime.



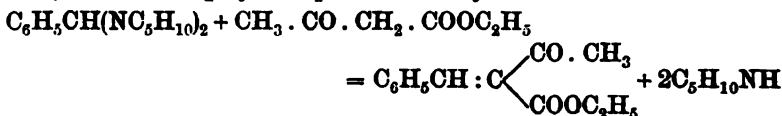
¹ *Annalen*, 1894, 281, 25; 1895, 288, 321.

² Vorländer, *Ber.*, 1895, 28, 2848.

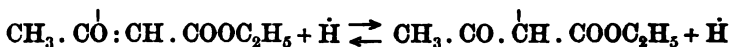
Knoevenagel explains the action of the condensing agent on the assumption that the aldehyde first unites with the base. Benzaldehyde and piperidine combine as follows:



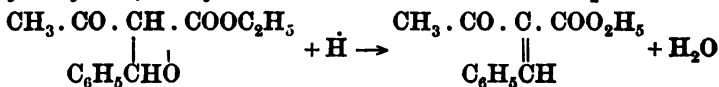
The product then interacts with the diketone and regenerates the base, which thus plays the part of a catalyst.



Another explanation based on ionisation has been advanced by Hann and Lapworth,¹ in which the acetoacetic ester forms an equilibrium mixture of the following ions:

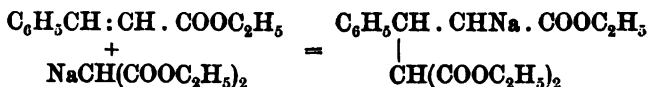


The latter would then combine with the molecule of benzaldehyde as neutral component (see p. 272), from which, by elimination of a hydroxyl ion, benzylidene-acetoacetic ester would be produced.



The effect of the base might be to remove hydrogen ions by forming the complex NRRH_2 or introduce hydroxyl ions and thus increase the concentration of the organic ions.

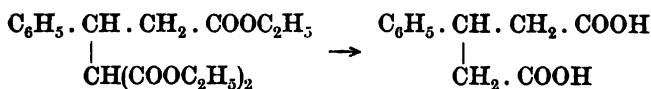
Michael's Reaction.² Michael has shown that the sodium compound of acetoacetic ester and malonic ester are capable of forming additive compounds with unsaturated compounds of the general formula $\text{R} \cdot \text{CH} : \text{CH} \cdot \text{X}$ or $\text{R} \cdot \text{C} : \text{C} \cdot \text{X}$, in which R is a positive or negative organic radical and X a strongly negative radical like a carbonyl or cyanogen group. The sodium joins the carbon atom attached to the most negative group and the negative radical, the positive carbon group. The first example studied by Michael was the condensation of sodium malonic ester (prepared by the action of metallic sodium or dry sodium ethoxide, on the ester dissolved in ether) on cinnamic ester. The union takes place in the following way:



¹ *Trans.*, 1904, 85, 46.

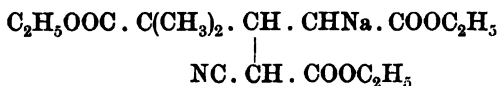
² Michael, *J. prakt. Chem.*, 35, 351; 43, 395; 45, 55; 49, 20; Auwers, *Ber.*, 1891, 24, 307, 2887; 1893, 26, 364; 1895, 28, 263; Ruhemann and Cunningham, *Trans. Chem. Soc.*, 1898, 73, 1006.

Acids liberate the tribasic ester which, by hydrolysis, can be converted into the dibasic acid,

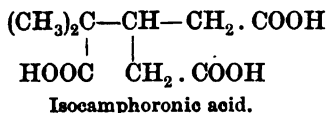


Fumaric, maleic, and citraconic esters, benzylidene acetone, acetylene dicarboxylic, phenylpropionic ester, &c., behave in the same way.

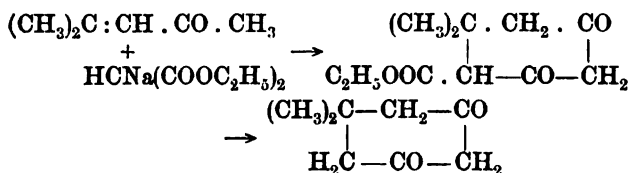
The sodium compound of cyanacetic ester resembles malonic ester¹ and has been utilized by W. H. Perkin, jun.,² for the synthesis of isocamphoronic acid. Dimethylglutaconic ester, when digested with an alcoholic solution of sodium cyanacetic ester, yields:



If the resulting ester is then hydrolysed, isocamphoronic acid is obtained, which consequently has the formula:



The same condensation process has also been applied to the synthesis of cyclic compounds. Vorländer³ obtained dimethyl diketocyclohexane from mesityl oxide as follows:



and Knoevenagel prepared isoacetophorone in the same fashion, using sodium acetoacetic ester in place of sodium malonic ester.

Knoevenagel⁴ also found that diethylamine could replace sodium or sodium ethoxide in effecting condensations of this character.

The Friedel-Crafts Reaction. The reaction discovered in 1877 by Friedel and Crafts,⁵ in which anhydrous aluminium chloride is the active agent, has had an extraordinarily wide and varied application in organic synthesis. It is connected more particularly with the

¹ Muller, *Compt. rend.*, 1892, 114, 1204.

² *Proc. Chem. Soc.*, 1900, 16, 214.

³ *Annalen*, 1896, 294, 253.

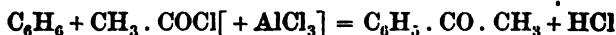
⁴ *Ber.*, 1904, 37, 4464.

⁵ *Compt. rend.*, 1877, 84, 1892; *Ann. Chim. Phys.*, 1884 (6), 1, 449.

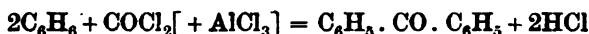
union of aromatic hydrocarbons with a variety of other organic compounds such as alkyl halides, acid chlorides, &c. *Hydrocarbons* can be obtained by combining an alkyl halide, e.g. methyl chloride, with benzene in presence of anhydrous aluminium chloride, when a vigorous evolution of hydrogen chloride occurs and toluene is formed.



Ketones can be prepared in the same way by using an aromatic hydrocarbon and an acid chloride. Benzene and acetyl chloride give acetophenone.

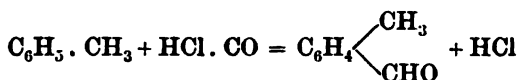


Carbonyl chloride and benzene react in a similar manner.

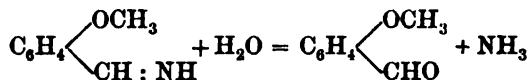
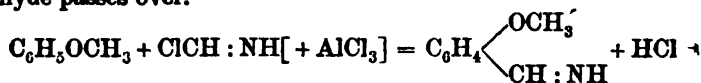


Aldehydes have been obtained by uniting an aromatic hydrocarbon with a mixture of carbon monoxide and hydrogen chloride in presence of dry cuprous chloride and aluminium chloride.¹

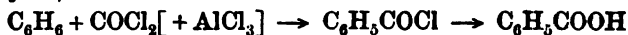
p-Tolylaldehyde has been prepared from toluene.



A better method was subsequently found for obtaining the aldehydes of phenols and phenol ethers by the use of the compound of hydrogen chloride and hydrogen cyanide. $\text{HCN} \cdot \text{HCl}$ is prepared *in situ* by passing the mixed gases into the phenol ether and aluminium chloride. The imino compound which is formed is acidified with hydrochloric acid and distilled in steam, when the aldehyde passes over.



Acids can be prepared either by the action of carbonyl chloride in the proportion required to give the acid chloride, which is then hydrolysed,



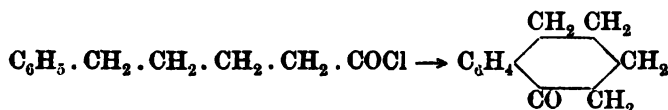
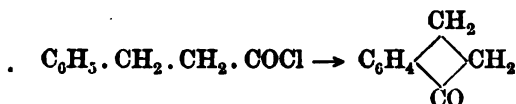
or by the action of chloroformamide, which is obtained by heating cyanuric acid in a current of hydrogen chloride, the vapours being

¹ Gattermann and Koch, *Ber.*, 1897, 30, 1622; *Annalen*, 1906, 347, 347.

then passed directly into the hydrocarbon containing aluminium chloride. The amide of the acid is finally hydrolysed.

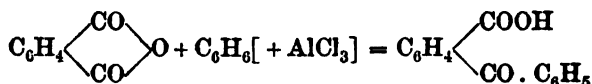


Aluminium chloride has also been used by Kipping¹ for effecting internal condensation in the case of phenylpropionyl chloride and phenylvaleric chloride in which ring formation occurs, the first giving rise to hydriindone,



and the second to benzocycloheptanone.²

In all the foregoing reactions a halogen compound is used in conjunction with the hydrocarbon, and hydrogen chloride is evolved. But aluminium chloride can also act as a condensing agent by virtue of its dehydrating action, and in other ways. Thus, phthalic anhydride and benzene condense to *o*-benzoyl benzoic acid:



Phenylcarbimide combines to form benzanilide,



and sulphur dioxide produces benzene sulphinic acid.



Reactions similar to the above can also be carried out with anhydrous ferric chloride, and in some cases, as in the union of benzene with benzyl chloride, a minute quantity of zinc or copper in powder, or the aluminium-mercury couple, will effect condensation.



Diphenylmethane.

It should be pointed out that the aluminium chloride occasionally reverses the process of condensation, for Jacobsen³ has shown that if

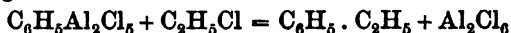
¹ *Trans. Chem. Soc.*, 1894, 65, 484; 1899, 75, 144.

² Kipping and Hall, *Proc. Chem. Soc.*, 1899, 15, 178.

³ *Ber.*, 1885, 18, 339.

hexamethylbenzene, to which a small quantity of aluminium chloride is added, is heated in a current of hydrogen chloride, methyl groups are successively detached, with the formation of penta-, tetra-, &c., methyl benzenes, and, finally, benzene. Another interesting fact connected with the reaction is the transference of methyl groups from one hydrocarbon to another under the influence of this reagent. Anschütz and Immendorff¹ obtained from toluene both benzene and *m*- and *p*-xylene.

Various theories have been advanced to explain these curious changes. Friedel and Crafts assumed the formation of an intermediate compound, $C_6H_5 \cdot Al_2Cl_6$, which united with the alkyl halide, regenerating aluminium chloride.



This would represent the chloride as a true catalyst, in which a small quantity would be sufficient to bring about the union of an indefinite amount of the reacting materials. In practice, this is not usually the case, for it is found that the amount of product increases approximately with the quantity of reagent. As Steele² has pointed out, this fact does not necessarily preclude the action of the aluminium chloride as a catalyst, provided it can be shown that it forms a stable compound with the product. The observations of Gustavson³ and others seem to point in this direction.

Gustavson has isolated a number of definite compounds of aluminium chloride and hydrocarbon, and aluminium chloride alkyl halide and hydrocarbon (possessing such formulæ as $Al_2Cl_6 \cdot C_6H_6$ and with ethyl chloride $Al_2Cl_6 \cdot C_6H_5(C_2H_5)_3 \cdot 6C_6H_6$), which appear to act as catalysts. From a dynamical study of the reaction, Goldschmidt and Larsen⁴ show that the condensation of anisol with benzyl chloride is a reaction of the first order, or unimolecular, and that the aluminium chloride acts as a catalyst, increasing the velocity of the reaction in proportion to its concentration. Steele concludes from similar observations 'that the action of aluminium and ferric chlorides in inducing the Friedel-Crafts reaction, differs from many cases of true catalysis only in the accident that these reagents combine with certain substances produced during the reaction and are thus removed from the system'. This view is also supported by the behaviour of the aluminium-mercury couple, of which a mere trace can effect rapid condensation between large quantities of benzene

¹ *Ber.*, 1885, 18, 657.

² *Trans. Chem. Soc.*, 1903, 83, 1490.

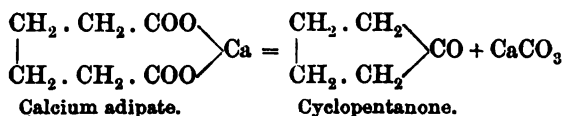
³ *Compt. rend.*, 1903, 136, 1065; 1905, 140, 940; J. W. Walker and Spencer, *Trans. Chem. Soc.*, 1904, 85, 1106.

⁴ *Zeit. phys. Chem.*, 1904, 48, 480.

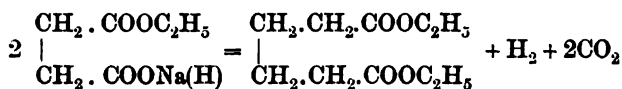
and certain aliphatic and aromatic halogen compounds like chloroform and benzyl chloride.¹

Other Condensation Processes. Condensation includes many processes which cannot be discussed in detail, but which should be remembered, such as the addition of hydrogen cyanide to aldehydes, ketones, and unsaturated ketones of the formula $R_2C:CR.CO.R$,² and the formation of ketones by distillation of the calcium or barium salts of organic acids, &c.

The latter reaction has been used to effect internal condensation by distilling the lime salt of a dibasic acid such as adipic or pimelic acid.³



The process of electrolysis may also effect condensation, when, for instance, sodium ethyl succinate is converted into adipic ester.⁴



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- Die synthetische Darstellungsmethoden der Kohlenstoff-Verbindungen*, by K. Elbs. Barth, Leipzig, 1889.
Synthetische Methoden der organischen Chemie, by T. Poesner. Leipzig, 1908.
Arbeitsmethoden für organisch-chemische Laboratorien, 8rd ed., by Lassar-Cohn. Voss, Hamburg, 1902.

¹ Hirst and Cohen, *Trans. Chem. Soc.*, 1895, 67, 826.

² Lapworth, *Trans.*, 1903, 83, 995; 1904, 85, 1206, 1214; 1906, 89, 945.

³ J. Wislicenus, *Annalen*, 1898, 275, 309.

⁴ Crum-Brown and Walker, *Annalen*, 1890, 261, 107.

CHAPTER VIII

THE CARBOHYDRATES

THE carbohydrates are among the principal products of plant life, and they are also elaborated, but to a much smaller extent, in the animal organism. They thus play an important rôle in the economy of nature. Whilst the study of their chemical history within the living organism belongs to the domain of the botanist and physiologist, their chemical behaviour, as denoting structure, claims the attention of the chemist.

The wide and abundant distribution of the vegetable carbohydrates, their extensive consumption as food, their employment in various industries, such as processes connected with fermentation and the manufacture of fabrics and paper, have given them an interest and value which attaches to no other group of compounds.

The carbohydrates include a number of substances, many of them being isomeric, which contain carbon, hydrogen, and oxygen. Though varying widely in physical properties—some, like cane and grape sugar, being sweet, soluble, and crystalline, whilst others, like starch and cellulose, are tasteless, insoluble, and non-crystalline—they are chemically closely related. For the majority of them contain hydrogen and oxygen in the proportion found in water, and hence their composition may be expressed by the general formula $C_x(H_2O)_x$, from which the term hydrate of carbon or *carbohydrate* is derived.

It should be added that several recently discovered sugars, for example, rhamnose, fucose, and chinovose (see p. 310), have the formula $C_6H_{12}O_6$ and form exceptions, but as the term has been generally adopted and still applies to the majority of these compounds, no serious objection can be raised to its use.

The more complex members of the carbohydrates are readily hydrolysed by acids or enzymes into one or more of the simpler members. Thus, starch and cellulose can be converted into glucose.



Classification of the Carbohydrates. The large number of these compounds, a number which has been greatly augmented within the

last two decades by the masterly researches of Emil Fischer, render it necessary for convenience of study to adopt some method of classification. They fall naturally into two classes, the sweet and crystalline compounds termed *sugars*, and the tasteless and non-crystalline. The non-crystalline carbohydrates possess a more complex structure than the crystalline; but the latter are also divisible into two groups having different molecular formulæ.

According to the old system of classification the carbohydrates were divided into three groups, one containing isomeric compounds of the formula $C_6H_{12}O_6$, termed glucoses or the grape-sugar group, a second containing compounds of the formula $C_{12}H_{22}O_{11}$ and termed saccharoses or cane-sugar group, and a third containing highly complex compounds of the general formula $(C_6H_{10}O_5)_n$, but of unknown molecular weight, termed amyloses or starch group. The old division is still retained, but the word glucose is now reserved for the dextro and laevo enantiomorphs of grape sugar, to replace the older word dextrose, which became unsuitable after the discovery of the laevo enantiomorph. For the same reason the word laevulose applied to fruit sugar, of which both dextro and laevo varieties are now known, has given place to fructose.

The three principal groups of carbohydrates are now distinguished by the names *monosaccharoses*¹ (formerly glucoses), *disaccharoses* (formerly saccharoses), and *polysaccharoses* (formerly amyloses).

After Fischer had succeeded in synthesising a number of new sugars containing more and less than six atoms of carbon, a further subdivision of the monosaccharoses became necessary. The new compounds, containing from two to nine carbon atoms, possess the general characters of monosaccharoses, and must be classified with them. They are distinguished by the names *biose*, *triose*, *tetrose*, &c. Thus, the group of monosaccharoses with six carbon atoms, to which grape and fruit sugar belong, will be termed *hexoses*. Whilst some of the monosaccharoses combine the properties of alcohols and aldehydes, others have the characters of alcohols and ketones, and the additional distinction *aldose* and *ketose* has been introduced. Thus, an aldehyde sugar containing six atoms of carbon would be termed an aldo-hexose, whilst the corresponding ketone compound would be a keto-hexose.

¹ E. Fischer uses the end syllable 'ide' (e.g. monosaccharide) in place of 'ose' by analogy with the glucosides which are structurally related to the cane-sugar group; but the termination has no significance when applied to members of the grape-sugar group, which are not anhydrides in the same sense that the glucosides are, and therefore the termination adopted above seems on the whole preferable.

Structure of the Monosaccharoses. Not more than a quarter of a century ago the monosaccharose group was represented by the four well-known sugars, grape sugar (glucose or dextrose), fruit sugar (fructose or laevulose), galactose, and sorbose. Three of the four substances, namely, glucose, fructose, and galactose, have been the subject of constant and careful study for years past, yet in spite of a vast accumulation of facts their true constitution remained obscure until the years 1885 and 1886, when Kiliani¹ obtained conclusive evidence of their structure.

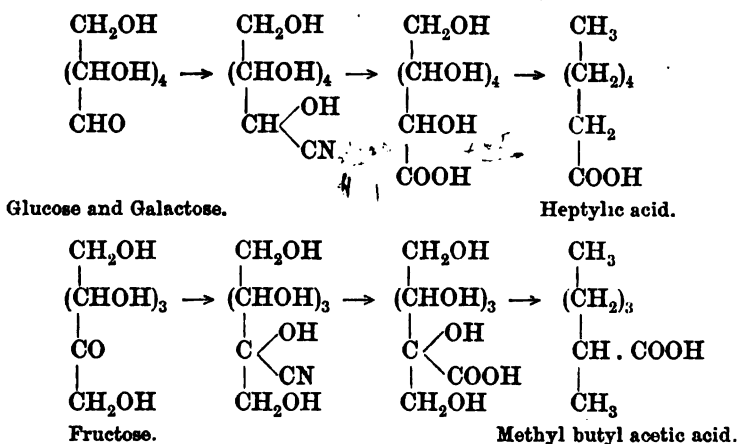
It had previously been shown that grape sugar, fruit sugar, and galactose yield penta-acetyl derivatives and therefore contain five hydroxyl groups. On reduction they take up two atoms of hydrogen and form hexahydric alcohols, which, with hydriodic acid, are converted into normal, secondary hexyl iodide. Consequently the three sugars consist of a normal chain of six carbon atoms. Five of these are probably present as carbinol groups, since it is unlikely that two hydroxyl groups are attached to one carbon atom. The sixth carbon atom will represent a ketone or aldehyde group; for the sugars undergo reduction and form additive compounds with hydrogen cyanide and combine with hydroxylamine and phenylhydrazine. They all behave more like aldehydes than ketones, inasmuch as they reduce alkaline copper sulphate and silver nitrate solutions; but, on the other hand, whilst glucose yields gluconic acid and galactose yields galactonic acid on oxidation, that is to say, substances which contain the same number of carbon atoms as the original sugars, fructose, under similar conditions, breaks up, and, among the products, trihydroxy-butyric acid has been identified.

The problem had advanced to this stage when Kiliani published his researches. He hydrolysed the cyanhydrins of glucose, galactose, and fructose, converting them into monobasic acids. They were then reduced with hydriodic acid. Glucose and galactose yielded the same normal heptylic acid, whereas fructose was converted into methyl butyl acetic acid. It was therefore assumed that glucose and galactose are aldehydes and fructose is a ketone, a view which until recently has been accepted. A new theory of their structure which involves the spatial configuration of the molecule has been brought forward by Lowry² and E. F. Armstrong³ and is discussed on p. 380.

¹ *Ber.*, 1885, 18, 3066; 1886, 19, 221, 767, 1128.

² *Trans. Chem. Soc.*, 1908, 83, 1814.

³ *Trans. Chem. Soc.*, 1908, 83, 1805.



The abnormal behaviour of fructose in reducing alkaline metallic salts, which is usually regarded as characteristic of aldehydes, is ascribed to the ready oxidizability of hydroxy-ketones. The case is similar to that of the hydroxy-acids, which like tartaric acid are easily oxidized and separate silver from ammonia-silver nitrate, whilst simple dibasic acids like succinic acid have no such action.

In the same year (1887) that Kiliani completed his researches on the constitution of glucose, galactose, and fructose, Emil Fischer¹ prepared the first artificial sugar in the pure state, which he named α -acrose. The substance proved to be the inactive representative of natural fructose. Then followed in quick succession the synthesis of ordinary or dextro-glucose and its optical enantiomorph, laevo-glucose, natural fruit sugar or dextro-fructose, and the corresponding laevo compound and a series of new artificial sugars. The stimulus given by Fischer to this line of research led to a more careful examination of the natural sugars, with the result that dextro-mannose, first prepared artificially by the oxidation of mannitol, was found to be somewhat widely distributed in nature. The monosaccharose group is now represented by sugars which contain from two to nine carbon atoms, members of all the stereoisomeric tetroses and pentoses, and twelve of the sixteen possible aldo-hexoses, in addition to the isomeric fructoses, sorboses, and other keto hexoses. The following is a list of the natural and artificial monosaccharoses at present known, all of which have been obtained artificially and their configuration accurately ascertained.²

¹ Ber., 1887, 20, 1093, 2566.

² Ber., 1894, 27, 3198.

	<i>Aldoses</i>	<i>Ketoses</i>
<i>Biose</i>	Glycollic aldehyde	
<i>Trioses</i>	Glyceric aldehyde	Dihydroxy-acetone
<i>Tetroses</i>	<i>d-l</i> -Erythrose	<i>d</i> -Erythrulose
	<i>l</i> -Threose	
<i>Methyl tetrose</i>	Rhamno tetrose	
<i>Pentoses</i>	<i>d-l</i> -Arabinose	<i>l</i> -Arabinulose
	<i>d-l</i> -Xylose	
	<i>l</i> -Ribose	
	<i>d</i> -Lyxose	
<i>Methyl pentoses</i>	Rhamnose	
	Chinovose	
	Fucose	
<i>Hexoses</i>	<i>d-l</i> -Glucose	<i>d-l</i> -Fructose
	<i>d-l</i> -Gulose	<i>d-l</i> -Sorbose
	<i>d-l</i> -Mannose	
	<i>d-l</i> -Idose	
	<i>d-l</i> -Galactose	<i>d</i> -Tagatose
	<i>d-l</i> -Talose	
<i>Methyl hexose</i>	Rhamnohexose	
<i>Heptoses</i>	<i>d-l</i> -Mannoheptose	
	α and β -Glucoheptose	
	α and β -Galaheptose	
<i>Methyl heptose</i>	Rhamnoheptose	
<i>Octoses</i>	Manno-octose	
	α -Gluco-octose	
	Gala-octose	
<i>Nonoses</i>	Mannononose	
	Glucononose	
<i>Aromatic series</i>	Phenyl tetrose	

A new and nearly complete chapter has thus been added to organic chemistry, the far-reaching effects of which it is still impossible to forecast. Meanwhile it has afforded a deeper insight into a group of compounds intimately associated with the main function of vegetable life, and at the same time provided a brilliant and convincing proof of the soundness of the van't Hoff-Le Bel hypothesis.

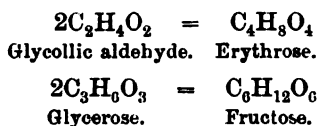
It is not intended to give an abstract of the voluminous literature which has been published on the subject of the monosaccharoses. To do so would be to defeat the object in view, namely, that of placing before the student such facts as will enable him

to clearly understand the synthetic methods for preparing these substances and the process by which their configuration has been ascertained.

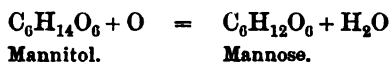
Natural Sources of the Monosaccharoses. Some of the monosaccharoses, like glucose and fructose, are found uncombined in plants and animals. These and others may also be obtained from other vegetable products—the glucosides and polysaccharoses—by the hydrolysing action of ferments or acids. Thus, *d*-glucose is found in amygdalin, salicin, populin, sinigrin, and in fact in the majority of glucosides, whilst rhamnose is found in quercitrin, fustin, &c., and together with galactose in xanthorhamnin. Among the polysaccharoses, cane sugar yields glucose and fructose; raffinose yields glucose, fructose, and galactose, and the cellulose of the ivory nut and other carbohydrates give mannose on hydrolysis.

Synthetic Preparation of the Monosaccharoses. The following synthetic methods have been devised for the preparation of the monosaccharoses and, unless otherwise stated, have been elaborated by Emil Fischer.¹

1. *Polymerisation, or Aldol Condensation, of the lower members of the group by the action of a solution of an alkali.* Glycollic aldehyde has been converted into erythrose and glycerose into fructose (p. 274).



2. *The Oxidation of the Polyhydric Alcohols.* This is effected by means of bromine in presence of sodium carbonate, of nitric acid, or of Fenton's reagent (hydrogen peroxide and a trace of ferrous salt). The product may be an aldehyde or ketone or a mixture of the two. Thus, glycerol gives glycerose (chiefly dihydroxyacetone), whilst mannitol gives the aldehyde, mannose.



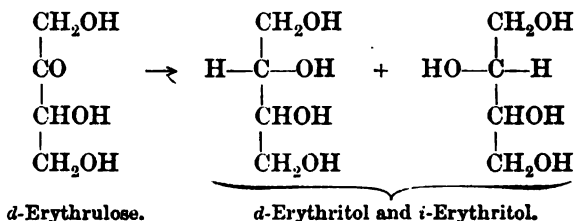
3. *The Oxidising action of Bertrand's 'sorbse bacterium'.* Here the ketose only results. Glycerol gives dihydroxyacetone, erythritol gives the ketone, erythrulose, arabitol forms arabinulose, sorbitol gives sorbose, mannitol gives fructose, and so forth.

¹ *Ber.*, 1890, 23, 2127; 1894, 27, 3190.

² *Ann. Chim. Phys.*, 1904 (8), 3, 181.

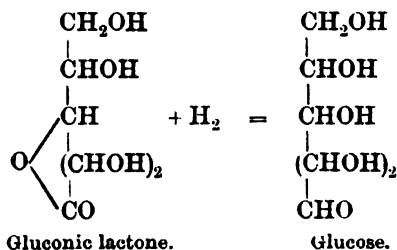
The action of the organism is selective, depending, as we shall see later (p. 827), on the configuration of the alcohol.

This method also serves the purpose of obtaining active polyhydric alcohols; for on reduction of the ketoses, formed by Bertrand's bacterium, a new asymmetric carbon atom is created which under the asymmetric conditions of its formation produces, or may produce, unequal quantities of active products. Thus, *d*-erythrulose gives on reduction *d*-erythritol as well as the meso product, whilst *d*-sorbose gives *d*-iditol along with *d*-sorbitol.

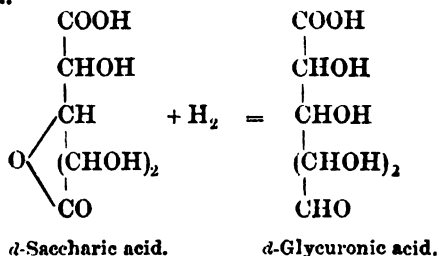


4. *The Reduction of the Lactones of Mono- and Di-basic hydroxy acids.* The process was devised by Fischer and is of very general application. It is effected by means of sodium amalgam in a solution maintained slightly acid by the addition of sulphuric acid. The object of keeping the solution acid is to prevent the hydrolysis of the lactone by the formation of the sodium salt which withstands reduction.

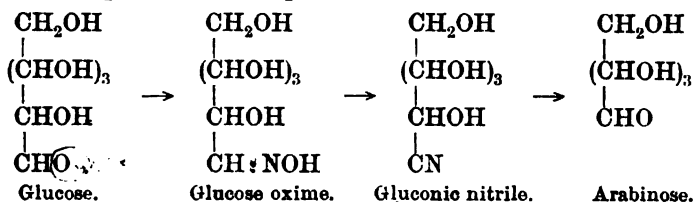
Gluconic lactone forms glucose.



d-Saccharic acid can be transformed in the same way into *d*-glycuronic acid.

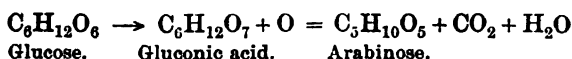


5. *Conversion of a Higher to a Lower Monosaccharose.* This is effected by a method which is due to Wohl¹ and consists in removing water and hydrogen cyanide in the following manner: The monosaccharose, for example, glucose, is converted into the oxime with hydroxylamine. The product is then acted upon with acetic anhydride in presence of sodium acetate, which removes a molecule of water and at the same time acetylates the hydroxyl groups, forming the nitrile of penta-acetylgluconic acid. Ammonia silver nitrate solution now removes hydrogen cyanide and gives the acetyl derivative of the pentose, from which, by the action of ammonia an acetamide derivative of the pentose is produced. Finally, by the action of sulphuric acid the pentose is liberated.

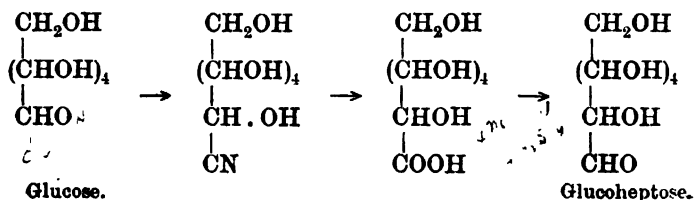


By this method glucose has been converted in successive stages into arabinose, erythrose, glycerose, and glycollic aldehyde.

6. Another method, due to Ruff,² produces a similar result. The monobasic acid obtained from the higher monosaccharose is oxidized by means of Fenton's reagent—hydrogen peroxide and a trace of ferrous salt—to the lower sugar. Gluconic acid from *d*-glucose has been converted into *d*-arabinose and *d*-arabinose into *d*-erythrose.



7. *Conversion of a Lower to a Higher Monosaccharose.* The method consists in producing the cyanhydrin of the lower sugar, converting the latter into the corresponding acid by hydrolysis and reducing the lactone as previously described (p. 309). Glucose has been converted into glucoheptose in this way.

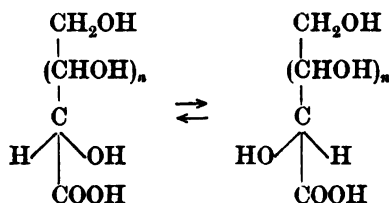


¹ Ber., 1898, 26, 780; 1897, 30, 3101; 1899, 32, 3666.

² Ber., 1898, 31, 1573.

It should be pointed out that in the process a new asymmetric carbon atom is introduced which may form two enantiomorphous arrangements and consequently give rise to two products. This is actually the case, for on turning to the table on p. 814 it will be seen that α - and β -glucoheptoses and α - and β -galaheptoses are formed from the corresponding hexoses. On the other hand only one product is obtained from mannose.

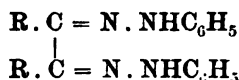
8. *Interconversion of Isomeric Aldoses.* The conversion of one monosaccharose into another has been effected in the following way: Fischer found that on heating the monobasic acids (derived from the sugars by oxidation) in aqueous solution with pyridine to a temperature of 180–150° a molecular change occurs. The hydrogen atom and hydroxyl group attached to the carbon atom next to the carboxyl group are interchanged and a new stereoisomeric modification is produced. It occasionally happens that the conversion is complete; but, as the process is reversible, the original and the newly formed product are as a rule present as an equilibrium mixture. The reaction is analogous to the conversion of active into racemic and meso tartaric acid when heated with water (see p. 80), and may be represented as follows:



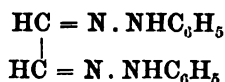
The addition of a weak base like pyridine prevents the formation of the lactone, which would interfere with the process of conversion. The method is capable of very general application, and has proved of the greatest value, not only in the synthesis of new sugars, but in affording an invaluable means of ascertaining their stereochemical relations. Among the pentoses, arabinose has been converted successively into arabonic acid, then by inversion into ribonic acid, and finally, by reduction of the lactone, into ribose. Xylose has been transformed in the same way into lyxose, whilst in the hexose group mannose has been converted into glucose and galactose into talose. Also a dibasic acid like mucic acid has been transformed into the stereoisomeric allomucic acid.

9. *Conversion of Aldose into Ketose.* The change of aldose to ketose may be effected by the aid of phenylhydrazine, a reagent which in the skilful hands of E. Fischer has proved invaluable, not only for its

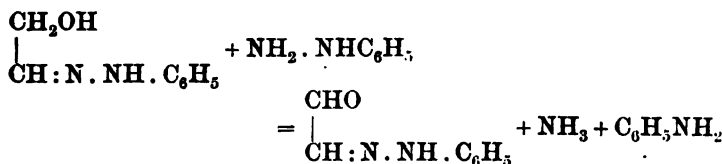
present object of converting one sugar into another, but in the more generally useful purpose of isolating, purifying, and identifying the mono- and di-saccharoses. All the ketose and aldose sugars combine with one molecule of phenylhydrazine, forming phenylhydrazones. These substances, with the exception of the hydrazone of mannose and a few of the higher members of the group, are very soluble in water. If, however, an excess of phenylhydrazine (at least three molecules), in the form of an aqueous solution of the acetate, is employed, an insoluble yellow crystalline substance is deposited, on warming, which is known as an osazone. Osazones are formed from all compounds containing a ketone and carbinol, aldehyde and carbinol, or two aldehyde or two ketone groups in juxtaposition, and have the general formula :



Thus, glycollic aldehyde and glyoxal give the same osazone ;



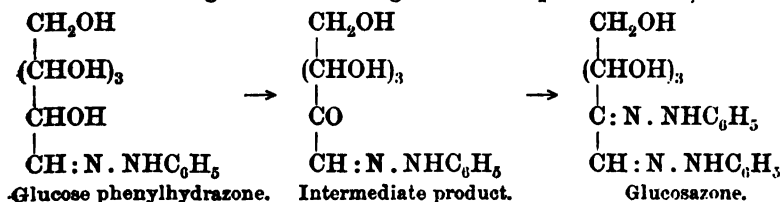
but in the former case the process takes place in two stages. The phenylhydrazone is first formed and then undergoes oxidation at the expense of a second molecule of phenylhydrazine, which thereupon breaks up into ammonia and aniline thus :



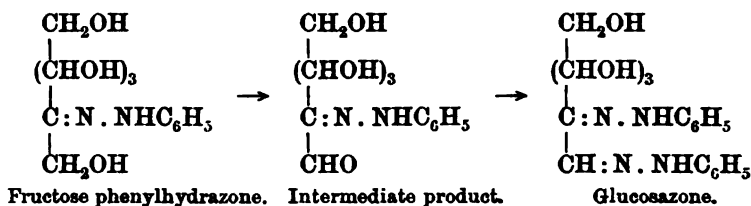
The aldehyde hydrazone then unites with another molecule of phenylhydrazine to form the osazone.



In the case of glucose the changes will be represented as follows :

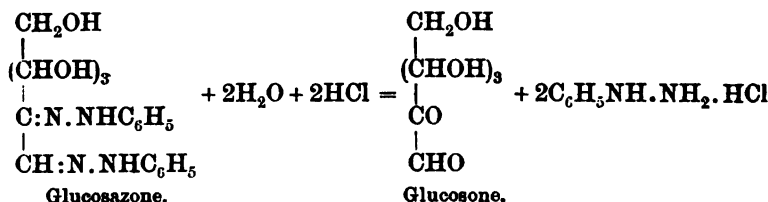


Fructose behaves in a similar fashion.

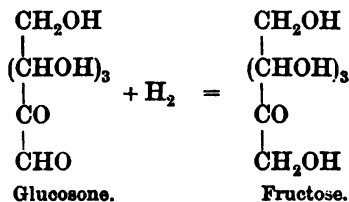


It should be noted that the products obtained from natural glucose and natural fructose are not isomeric but identical, a point of some importance in connection with their space configurations.

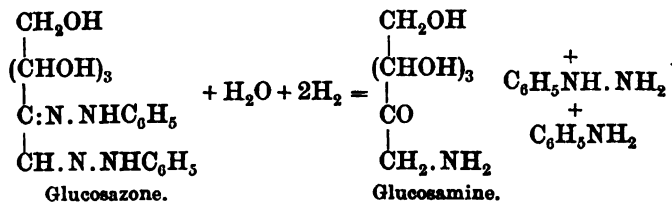
Now if the osazone is warmed for a moment with strong hydrochloric acid it is hydrolysed and forms a ketonic aldehyde, which is known as an *osone*, and two molecules of phenylhydrazine are removed.



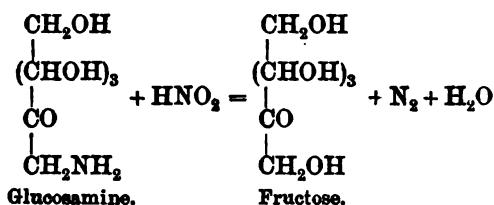
The osone can be isolated in the form of its lead compound, and gives, on reduction with zinc dust and glacial acetic acid, a ketose. In this way glucosone can be converted into fructose.



Another way of compassing the same end is to reduce the osazone with zinc dust and acetic acid when an *osamine* is formed.

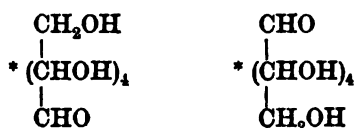


The latter on treatment with nitrous acid then forms the ketose.

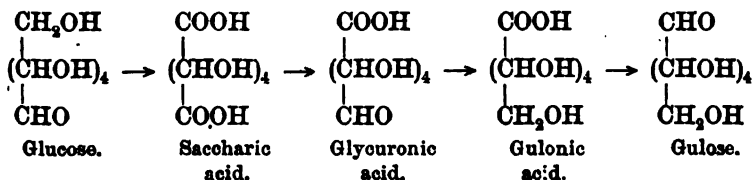


10. *Conversion of Ketose into Aldose.* The only way of producing this change is through the alcohol in the following steps: ketose $\rightarrow$ alcohol $\rightarrow$ aldehyde. Thus, fructose on reduction yields a mixture of sorbitol and mannitol, which on oxidation form respectively glucose and mannose. The polyhydric alcohols, it should be added, can be purified in some cases by Meunier's method, which consists in combining the alcohol with benzaldehyde and thus forming a crystalline benzylidene derivative.

11. *Inversion of Stereoisomeric Aldoses.* This has been effected by Fischer by the graduated reduction of the dibasic acids. Its significance will be more apparent when the question of configuration is considered. It will be clear, however, that, if the four asymmetric carbon atoms present in glucose have different values, a new stereoisomeric sugar will be formed by interchanging the end carbinol and aldehyde group.



If the lactone of saccharic acid is reduced it forms first the aldehyde acid, viz. glycuronic acid, then gulonic acid, in which the original aldehyde becomes a carbinol group; if the lactone of gulonic acid is further reduced, the inverse arrangement of carbinol and aldehyde is finally effected, and the product is known as gulose.



12. *Interconversion of Aldoses and Ketoses.* Lobry de Bruyn and

* The four asymmetric carbon atoms.

van Ekenstein¹ found that under the influence of alkalis, alkaline earths, sodium acetate, lead oxide, &c., the hexoses are slowly transformed into mixtures of their isomers. Each of the hexoses, glucose, fructose, and mannose, forms under these conditions a certain proportion of the other two, together with certain other sugars, e. g. glucose, which is also found in molasses. Galactose under similar conditions yields talose and also two ketoses, ψ -tagatose which has been identified as *l*-sorbose, and *d*-tagatose which gives the same osazone as *d*-galactose. ψ -Fructose is obtained in the same way from ordinary fructose. The explanation of these changes will be discussed later.

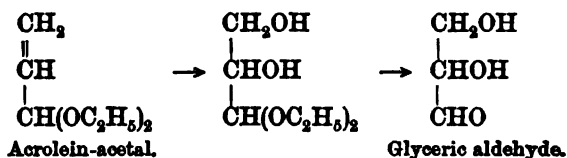
The following is a short account of the principal monosaccharoses.

Biose. Glycollic aldehyde is the only biose. Fischer originally prepared it in an impure state by the action of cold baryta water on bromacetaldehyde. More recently Fenton² has obtained it in the crystalline form by heating dihydroxymaleic acid with water to 60°.



It gives the general reactions of the sugars, and with sodium hydroxide polymerises to a tetrose.

Trioses. A mixture of glyceric aldehyde and dihydroxyacetone was obtained by Fischer and Tafel by oxidising glycerol with dilute nitric acid or with bromine and sodium carbonate. It forms a syrup which polymerises in presence of sodium hydroxide solution, yielding α -acrose (see p. 811). Pure glyceric aldehyde was subsequently obtained by Wohl³ on carefully oxidising acrolein-acetal with cold permanganate and then hydrolysing.



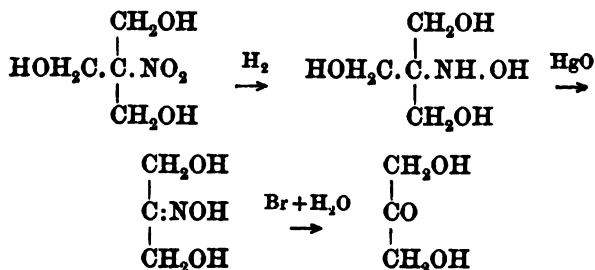
Although glycerose contains an asymmetric carbon atom and should exist in two enantiomorphous forms, no optically active substance has yet been isolated. Glyceric aldehyde is characterized by the formation of an insoluble crystalline substance with phloroglucinol dissolved in hydrochloric acid, which the ketone does not

¹ *Ber.*, 1895, 28, 8078; *Rec. trav. chim. Pays. Bas.*, 1900, 19, 1.

² *Trans. Chem. Soc.*, 1894, 65, 899; 1895, 67, 48, 774; 1896, 69, 546; 1897, 71, 375.

³ *Ber.*, 1898, 31, 1796, 2894; 1900, 33, 8095.

give. Dihydroxyacetone has been obtained by Piloty¹ from formaldehyde and nitromethane in the following way. Condensation of three molecules of aldehyde with one of nitromethane is first effected:



Careful reduction converts the nitro compound into the hydroxylamine derivative, and subsequent oxidation with mercuric oxide yields the oxime of dihydroxyacetone, which is then liberated by oxidation with bromine and water. The ketone is also obtained by the action of Bertrand's *sorbose bacterium* on glycerol (see p. 299).

Tetroses. An impure product was originally obtained by the oxidation of erythritol (a tetrahydric alcohol found in certain lichens) and also by the polymerisation of glycollic aldehyde. Both products were inactive. More recently Wohl and Ruff have been successful in obtaining three of the four possible active forms from the active pentoses. Thus the tetrose known as *l*-threose was obtained by Wohl² from *l*-xylose, and *l*-erythrose from *l*-arabinose, whilst Ruff³ prepared *d*- and *l*-erythrose by oxidation of *d*- and *l*-arabonic acid. All the tetroses yield erythritols on reduction and mono- and di-basic acids on oxidation. Whereas the tetroses contain two dissimilar asymmetric carbon atoms, and can therefore form two pairs of enantiomorphs, the alcohols and dibasic acids (tartaric acids), which contain two similar asymmetric carbon atoms, can only produce two active (racemic) and one meso form. Natural erythritol represents the meso form, for it is obtained by the reduction of *d*- and *l*-erythrose, which in turn yield mesotartaric acid on oxidation, whilst Griner's⁴ erythritol, which he prepared from butadiene tetrabromide, is the racemic modification. The following table represents these relations; where the source is not mentioned it implies that the substance is obtained from the most closely related product by oxidation or reduction.

¹ Ber., 1897, 30, 3161.

² Ber., 1899, 32, 3672.

³ Ber., 1899, 32, 3666.

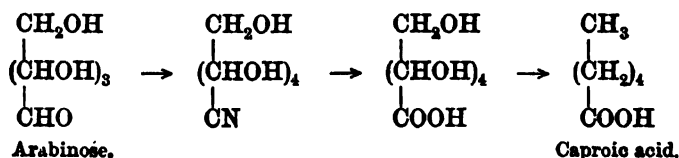
⁴ Compt. rend., 116, 723; 117, 558.

Tetroses.

Tetritol.	Aldo-tetrose.	Tetronic acid.	Tartaric acid.
<i>i</i> -erythritol (natural)	$\left\{ \begin{array}{l} d\text{-erythrose} \\ \text{(from } d\text{-arabinose)} \\ l\text{-erythrose} \\ \text{(from } l\text{-arabinose)} \end{array} \right.$	$\left\{ \begin{array}{l} d\text{-erythronic acid} \\ - \\ - \end{array} \right.$	<i>i</i> -tartaric acid
<i>d</i> -erythritol (from erythrulose)	—	—	<i>d</i> -tartaric acid
<i>l</i> -erythritol	<i>l</i> -threose (from <i>l</i> -xylose)	—	<i>l</i> -tartaric acid

In addition to the above there is a methyl tetrose which has been prepared by Wohl's method from rhamnose, and a phenyl tetrose which Fischer and Stewart¹ obtained from phenyltrihydroxybutyric lactone by reduction.

Pentoses. The pentoses contain three asymmetric carbon atoms, and can therefore exist in eight stereoisomeric forms. Of these six are known, *d*- and *l*-arabinose, *l*-ribose, *d*- and *l*-xylose, and *d*-lyxose. *l*-Arabinose is a vegetable product and was first obtained in 1869 by Scheibler, who gave it the formula $C_5H_{12}O_5$ and included it among the glucoses. Subsequently Kiliani², by a careful analysis of the osazone, showed conclusively that it had the formula $C_5H_{10}O_5$ and was a pentose. He also prepared the cyanhydrin, and by hydrolysis, followed by reduction, transformed it into normal caproic acid, a further proof of the correctness of his analytical results.

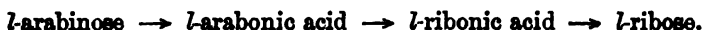


Arabinose is prepared from gum-arabic and certain other vegetable gums by boiling with dilute sulphuric acid, precipitating the acid with lime, filtering, evaporating to dryness, and extracting the residue with alcohol. On evaporation of the alcohol, arabinose crystallizes in colourless needles which are strongly dextrorotatory in solution. Arabinose is therefore not present as such in the gum, but in a higher complex known as a pentosan, which probably bears the same relation to arabinose that starch does to glucose. It may appear anomalous to denote by the expression '*l*-arabinose' a strongly dextro-

¹ Ber., 1892, 25, 2555.² Ber., 1887, 20, 839.

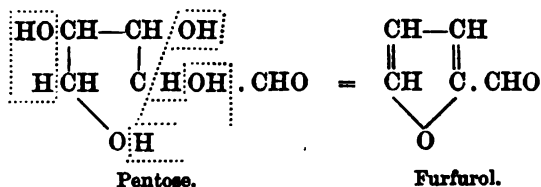
rotatory compound ; but it must be remembered that the terms laevo and dextro, when applied to the sugars, have lost their original meaning, being no longer used to indicate optical character but stereoisomeric relations, in accordance with a suggestion of Fischer. Since, as we shall shortly see, ordinary arabinose is directly related to *l*-glucose, the former, in spite of its dextro-rotatory character, is termed *l*-arabinose. The optical enantiomorph, *d*-arabinose, is obtained from grape sugar by Wohl's method.

Ribose, the third isomer, is prepared by the reduction of ribonic lactone, the latter being obtained by inversion from *l*-arabonic acid by heating with pyridine in the manner already indicated.



A second naturally occurring pentose is known as *l*-xylose and was discovered in 1886 by F. Koch. It is isomeric with arabinose and is prepared from wood-gum, a substance which forms part of the woody cell-wall of many plants ; *d*-xylose is obtained by Wohl's method from *d*-gulose. Lyxose, the sixth isomer, is obtained from xylose in precisely the same manner as that by which ribose is derived from arabinose. It has also been prepared from *d*-galactose by Wohl's method. In determining the configuration of the sugars, it is of fundamental importance to remember that ribose and xylose give different but inactive trihydroxyglutaric acids on oxidation, whilst those from *d*- and *l*-arabinose are active.

The pentose sugars are readily distinguished from the other monosaccharoses by boiling with strong hydrochloric acid, which converts them into furfural. The change may be represented thus :



Tollens' reagent (a solution of phloroglucinol or orcinol in strong hydrochloric acid, producing, on warming, a deep cherry-red or violet coloration according to the phenol used) is a useful qualitative test for a pentose.

The following table contains a list of the known pentoses and substances related to them.

Pentoses.

Pentitol.	Aldo-Pentose.	Pentonic acid.	Trihydroxy-glutaric acid.
<i>i</i> -xylitol	{ <i>l</i> -xylose (natural) <i>d</i> -xylose (from <i>d</i> -gulose) <i>d</i> -lyxose (from <i>l</i> -xylonic acid and <i>d</i> -galac- tose)	<i>l</i> -xylonic acid	{ <i>i</i> -trihydroxy-glu- taric acid <i>m. p.</i> 152°
<i>d</i> -arabitol		<i>d</i> -lyxonic acid	
—	—	—	—
<i>d</i> -arabitol	<i>d</i> -arabinose (from <i>d</i> -glucose)	<i>d</i> -arabonic acid	<i>d</i> -trihydroxy-glutaric acid <i>m. p.</i> 127°
<i>l</i> -arabitol	<i>l</i> -arabinose (natural and from <i>l</i> -glucose)	<i>l</i> -arabonic acid	<i>l</i> -trihydroxy-glutaric acid <i>m. p.</i> 127°
<i>i</i> -adonitol (from adonis ver- nalis (Merck))	<i>l</i> -ribose (from <i>l</i> -arabinose)	<i>l</i> -ribonic acid	<i>i</i> -trihydroxy-glutaric acid <i>m. p.</i> 170-171°

Several methyl pentoses are known and are found in the table on p. 298. They include *rhamnose*, a constituent of various glucosides (p. 299); *fucose*, which is found as a glucoside in seaweed; and *chinovose*, which occurs as an ethyl glucoside in chinovite. All three substances, on heating with hydrochloric acid, are converted into methyl furfural.

Hexoses. The properties of the hexoses are included in the general account of the monosaccharoses already given. They differ, however, from the majority of the other sugars of the group in two important respects. When boiled with dilute mineral acids they form levulinic acid, and together with glycerose and manno-nonose are the only sugars which undergo fermentation with yeast. The subject of fermentation is more fully discussed on p. 387.

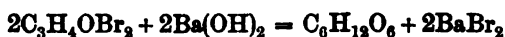
The history of the synthesis of the hexoses begins with an observation of Butlerow¹ in the year 1861. He found that by the addition of lime-water to a hot solution of trioxymethylene (a solid substance produced by the polymerisation of formaldehyde) *methylenitan* is formed, which is described as a sweet yellow syrup, giving the ordinary reactions for sugar, but optically inactive and incapable of fermentation. A considerable advance was made when Loew² discovered that formaldehyde and lime-water at the ordinary temperature yield a sweet syrup of the formula $C_6H_{12}O_6$, which he termed *formose*; but this also was unfermentable. A special interest attaches to this reaction, since it gave substantial support to a theory advanced

¹ *Annalen*, 1861, 120, 295; *Compt. rend.*, 1861, 53, 145.

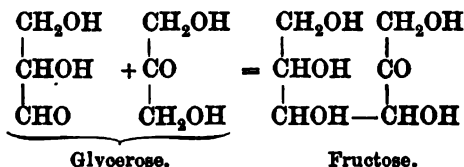
² *J. prakt. Chem.*, 1866, 33, 321.

by Baeyer,¹ that the carbon dioxide, assimilated by the plant as starch or sugar, may pass through the stage of formaldehyde. Shortly afterwards Loew² modified his method by replacing the lime by magnesia, and obtained a syrup which underwent fermentation. The new product was called *methose*. All three substances appear from Fischer's subsequent investigations to be complex mixtures containing α -acrose which Fischer and Tafel³ had meantime obtained in a state of purity by entirely different methods.

By the action of baryta on acrolein bromide a mixture was obtained from which two sugars, named α - and β -acrose, were isolated in the form of their osazones.



This method was afterwards modified by substituting glycerose (obtained from glycerol by oxidation (p. 299)), which, under the action of dilute alkali, polymerises.⁴ The product is a syrup from which α -acrose can be separated in the form of the crystalline osazone. α -Acrose was subsequently identified as inactive fructose, and the reaction was explained by Fischer as taking place in the following way:



As, according to Wohl⁵, little, if any, glyceric aldehyde is present in Fischer's glycerose, which consists, therefore, almost wholly of dihydroxyacetone, the action of the alkali must produce intramolecular change in the ketone. The process by which a ketose is transformed into an aldose is quite consistent with observations of Lobry de Bruyn, who noticed that any one of the sugars, fructose, glucose or mannose, forms under the influence of an alkali an equilibrium mixture of the three (see p. 332). The α -acrosazone, which was separated from Fischer's product, and closely resembled glucosazone, was converted into the osone and finally into the pure ketose. The latter proved to be the inactive form of fructose. By partial fermentation with yeast the dextro-enantiomorph or ordinary fructose is consumed, and laevo fructose remains and may be separated. On reduction of inactive fructose, inactive mannitol is formed which, on oxidation,

¹ Ber., 1870, 3, 67.

² Ber., 1887, 20, 1093, 2568.

³ Ber., 1889, 22, 475.

⁴ Ber., 1887, 20, 8884.

⁵ Ber., 1900, 33, 3095.

yields inactive mannose and inactive mannonic acid. The latter can be separated into the optical enantiomorphs by fractional crystallization of the strychnine or morphine salts. Thus a *d*- and *l*-mannonic acid are produced, each of which undergoes molecular change on heating with pyridine, being transformed respectively into *d*- and *l*-gluconic acid. The lactones of all the four acids can, on the one hand, be reduced to the corresponding sugars or, on the other, oxidised to the dibasic saccharic acids. In this way two mannoses, two glucoses, and four saccharic acids were prepared artificially by Emil Fischer. Natural fructose, although laevo-rotatory, is *d*-fructose, since it is related to *d*-glucose; for both *d*-glucose and ordinary fruit sugar yield the same *d*-glucosazone, and the latter can be converted through the osone into ordinary fructose (p. 804). The same *d*-glucosazone is also given by *d*-mannose, which consequently may be likewise converted into ordinary fructose.

This close relationship between the three natural sugars, *d*-glucose, *d*-fructose and *d*-mannose, has a peculiar interest from the fact of their occurrence side by side in nature as well as from their stereochemical connection, which will be discussed presently. The tabulated scheme on p. 818 represents the various synthetic steps described above. The sugars are in thick type.

In addition to the two glucoses and two mannoses, eight other stereoisomeric aldoses are known, together with their reduction and oxidation products and numerous other derivatives. They have been obtained as follows:

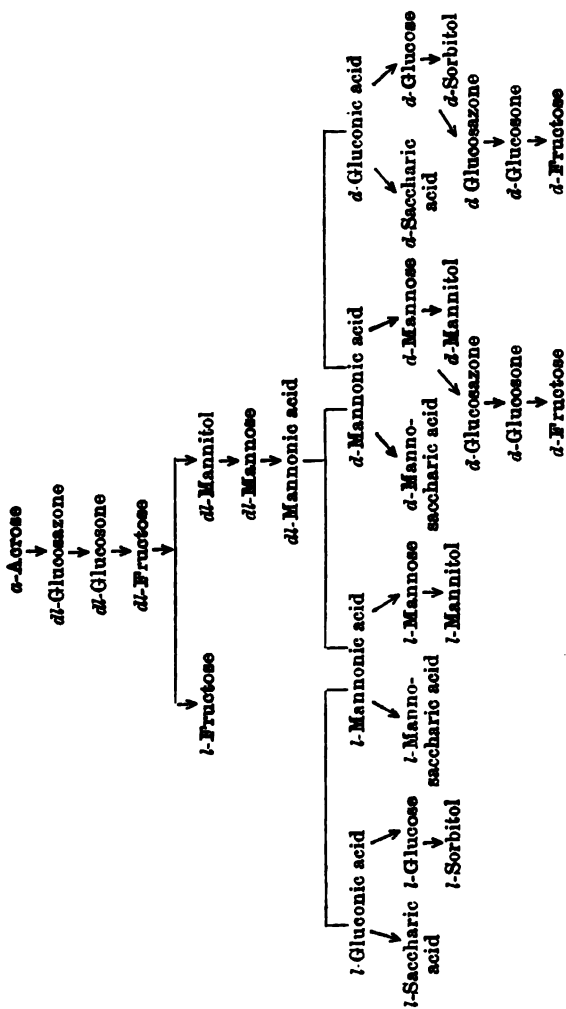
d-, *l*-Gulose were prepared by the inversion of *d*- and *l*-glucose by oxidation to the saccharic acids and subsequent reduction as described on p. 805.

d-, *l*-Idose were obtained from *d*- and *l*-gulonic acid, which, by inversion with pyridine, yield the corresponding *d*- and *l*-idonic acids. *l*-Idonic acid can also be obtained with *l*-gulonic acid from *l*-xylose, which forms the stereoisomeric cyanhydrins (see p. 815).

d-, *l*-Galactose. If natural or *d*-galactose from milk-sugar is oxidised, it yields meso-mucic acid. If the lactone of the latter is reduced, monobasic galactonic acid is formed, which is racemic and can be resolved into its enantiomorphs by the aid of the strychnine salt.

Each of the active galactonic acids yields an active galactose on reduction.

d-, *l*-Talose. *D*- and *l*-galactonic acid are converted by inversion with pyridine into *d*- and *l*-talonic acid, which on reduction give *d*- and *l*-talose. Each of these sugars gives a talomucic acid on oxidation. The laevo acid has also been obtained by the oxidation



The synthesis of the Sugara.

of β -rhamnohexonic acid (p. 824). Allomucic acid, which is not yet represented by any sugars, was prepared from mucic acid by inversion with pyridine.

The following table contains a list of hexoses and related compounds.

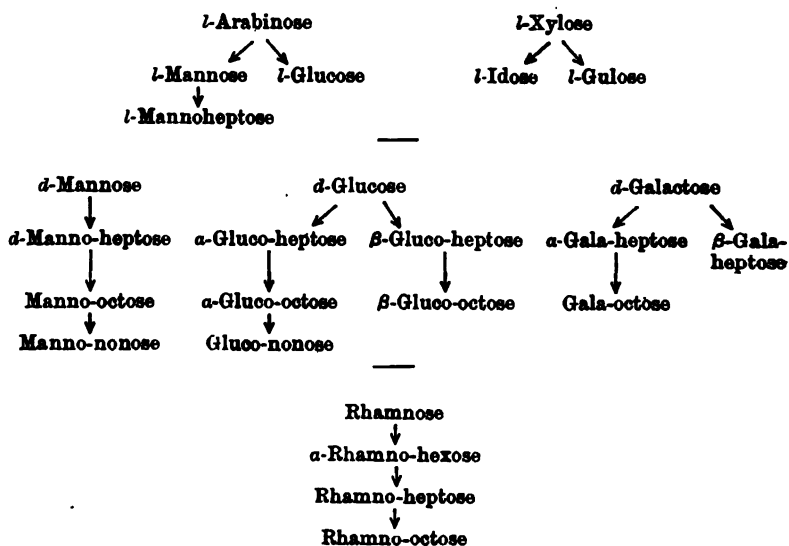
Aldo-hexoses.

Hexitol.	Aldo-hexose.	Hexonic acid.	Tetroxyadipic acid.
<i>d</i> , <i>l</i> -Mannitol	<i>d</i> , <i>l</i> -Mannose	<i>d</i> , <i>l</i> -Mannonic acid	<i>d</i> , <i>l</i> -Manno-saccharic acid
<i>d</i> , <i>l</i> -Iditol	<i>d</i> , <i>l</i> -Idose	<i>d</i> , <i>l</i> -Idonic acid	<i>d</i> , <i>l</i> -Ido-saccharic acid
<i>d</i> , <i>l</i> -Sorbitol	<i>d</i> , <i>l</i> -Glucose	<i>d</i> , <i>l</i> -Gluconic acid	<i>d</i> , <i>l</i> -Saccharic acid
<i>i</i> -Dulcitol	<i>d</i> , <i>l</i> -Gulose	<i>d</i> , <i>l</i> -Gulonic acid	<i>i</i> -Mucic acid
<i>d</i> , <i>l</i> -Talitol	<i>d</i> , <i>l</i> -Galactose	<i>d</i> , <i>l</i> -Galactonic acid	<i>d</i> , <i>l</i> -Talomucic acid
—	<i>d</i> , <i>l</i> -Talose	<i>d</i> , <i>l</i> -Talonic acid	<i>l</i> -Allomucic acid
—	—	—	—

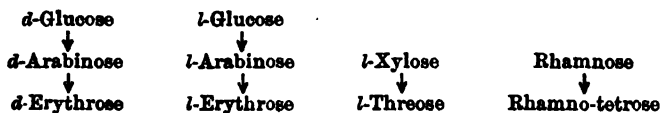
Keto-hexoses.

<i>d</i> -Mannitol	<i>d</i> -Fructose	—	—
<i>d</i> -Sorbitol	<i>l</i> -Fructose	—	—
<i>d</i> -Sorbitol	<i>d</i> , <i>l</i> -Sorbse	—	—
	<i>d</i> -Tagatose	—	—

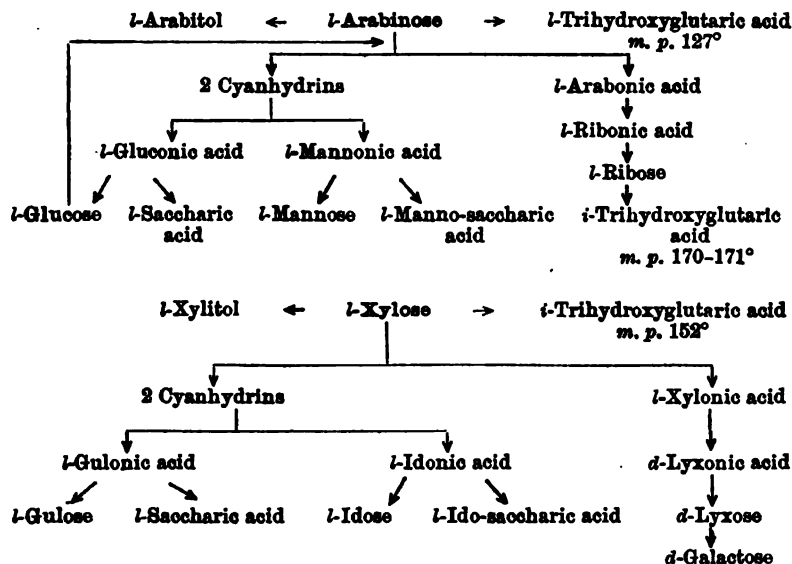
The following tables represent the synthesis of the higher from the lower sugars by Fischer's cyanhydrin method.



The sugars obtained by the degradation methods of Wohl and Ruff are represented as follows:



Configuration of the Aldo-Hexoses.¹ Before attempting to ascertain the space configuration of the large number of sugars which have been mentioned, it will be necessary to consider carefully the relation in which they stand to one another. This mutual relationship will be readily understood by reference to the tables given below. In the one the starting-point is arabinose, which is known in both laevo and dextro forms. From the laevo compound a set of laevo derivatives would result, whilst the dextro compound would produce dextro derivatives. In the second scheme xylose forms the starting-point. In both cases the laevo compound alone has been employed.



If it were possible to prepare glycollic aldehyde in quantity and build up the sugars in successive stages from it, by means of the cyanhydrin reaction, all the stereoisomers would probably be obtained and their configuration could be determined without difficulty. Let us attempt an imaginary scheme of this kind, adopting Meyer and

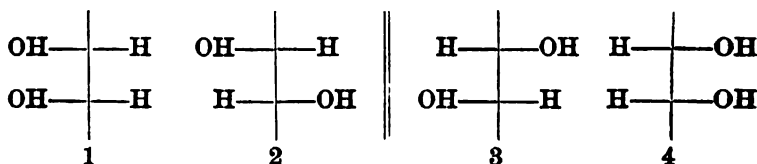
¹ E. Fischer, *Ber.*, 1894, 27, 3208; *Lehrbuch der Stereochemie*, p. 90, by A. Werner.

Jacobson's plan of representing the space arrangement of the isomeric aldoses by projection formulae (see p. 78). If we further assume that the aldehyde group is always at the bottom and the primary carbinol group at the top, we can omit these two groups, and merely represent the asymmetric carbon atoms with their hydroxyl and hydrogen appendages, the formulae being further simplified by denoting the asymmetric carbons by cross lines.¹

Starting with glycollic aldehyde and converting this, by the imaginary process referred to, into the next higher sugar, two stereoisomeric trioses will be obtained, since one asymmetric carbon is present, which may be denoted thus:



These will be optical enantiomorphs and form together an inactive or racemic combination. Each triose will yield two derivatives forming four tetroses, according to the general formula 2^n where n is the number of asymmetric carbon atoms (p. 88). They may be represented by adding on OH and H in inverse order below the first two groups in the trioses.



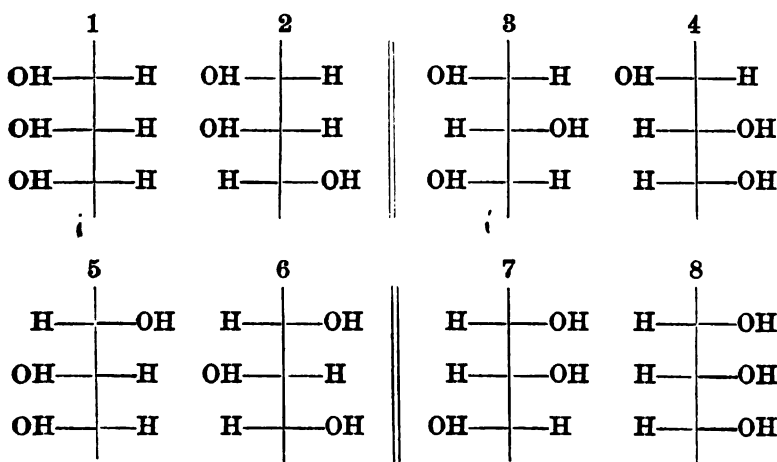
These four stereoisomers form two pair of optical enantiomorphs, namely, 1 and 4 and 2 and 3. Suppose now that the end groups in these compounds, instead of being different, are made identical, either by reduction to the corresponding alcohol, or by oxidation to the dibasic acid; the stereoisomers 1 and 4 become identical and represent the inactive meso variety. This is easily seen by revolving one of the two through 180° in the plane of the paper. The number of stereoisomers is now reduced to three according to the formula,

$$2^{\frac{n}{2}-1} (2^{\frac{n}{2}} + 1),$$

which is the general expression for the number of stereoisomers in a symmetrical molecule containing an even number of asymmetric carbon atoms. Thus, there are three tartaric acids and three ery-

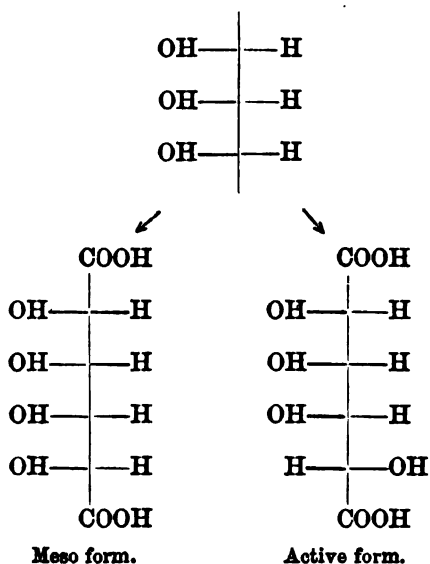
¹ Some chemists prefer to denote the position of the hydroxyl on the right or left by + or -. This system has not necessarily any reference to the optical character of the substance.

thritols, two being active enantiomorphs and the other an inactive meso compound. All these substances are known and are given in the table on p. 808. It follows from what has been said that *d*- and *l*-erythrose correspond to configurations 1 and 4, since they yield *mes*-erythritol and *mes*-tartaric acid on reduction and oxidation, whilst *l*-threose corresponds to the configuration 2 or 8. Since it is impossible to ascertain which of the two configurations represents the actual grouping in *l*-threose, it is customary to make an arbitrary choice in the case of *d*- and *l*-glucose and to derive all the other configurations from them. We must therefore first ascertain the configuration of these sugars. Continuing the process of imaginary synthesis, the four tetroses will each yield a pair of pentoses, making eight stereoisomers.



The optical enantiomorphs will be 1, 8; 2, 7; 3, 6; 4, 5. We will now follow the same line of inquiry pursued in the case of the tetroses and suppose the end groups (by reduction to pentitols or by oxidation to trihydroxyglutaric acids) to become identical. The number of stereoisomers is now reduced to four; for 1 = 8; 2 = 4; 3 = 6; 5 = 7. Which of these four pairs are active and which meso? It is now evident that with two similar end groups the middle carbon atom is no longer asymmetric in the usual meaning of the term. The activity is therefore determined by the two outer asymmetric carbon atoms. It follows that 1, 8 and 3, 6 are meso, and 2, 7 and 4, 5 are active forms when the end carbon groups are the same. We are now in a position to assign configurations to the six pentoses which have been described.

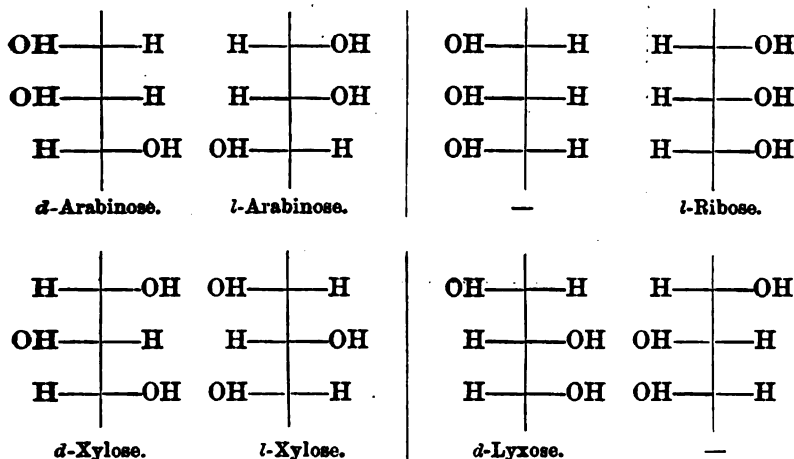
If we refer to the tables on p. 315, we notice that two of the pentoses, *l*-xylose and *l*-ribose, give inactive trihydroxyglutaric acids on oxidation. They will therefore be represented by one from each pair of the configurations 1, 8 and 3, 6. But *l*-xylose has been converted into two active saccharic acids, *l*-saccharic and *l*-ido-saccharic acid (see table, p. 315). The configuration of *l*-xylose cannot therefore be represented by 1, 8, since either enantiomorph would yield one inactive, internally compensated saccharic acid.



Consequently *d*- and *l*-xylose will be 3, 6 and *l*-ribose will be 1 or 8. The same process of reasoning may be applied to arabinose and lyxose, which give active dibasic acids, and therefore have configurations 2, 7 and 3, 6. It can be shown that one of the pair of saccharic acids derived from the 4, 5 configuration is a meso acid and cannot therefore represent arabinose, which gives two active saccharic acids. As ribose is obtained from arabinose by the interchange of the hydrogen and hydroxyl attached to bottom carbon atoms, *d*- and *l*-arabinose will have the configurations 2, 7. Lyxose, which is derived in the same way from xylose, will represent the fourth pair, 4, 5. As both *l*-arabinose and *l*-xylose are directly connected with *l*-glucose, the arbitrary configuration assigned to the latter (p. 321) will determine that of the two former as well as of all the other pentoses.

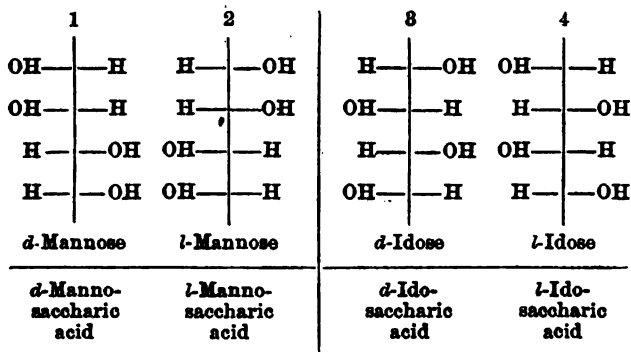
CONFIGURATION OF THE MONOSACCHAROSES 319

The configurations of the pentoses will stand as follows :

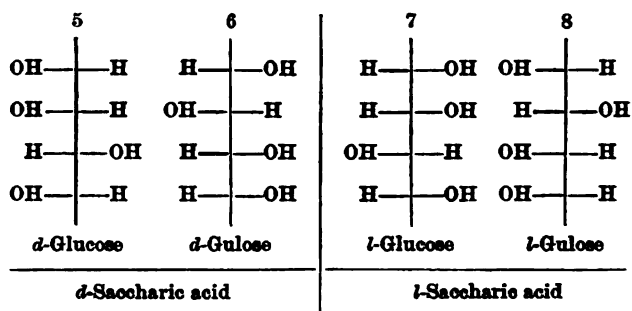
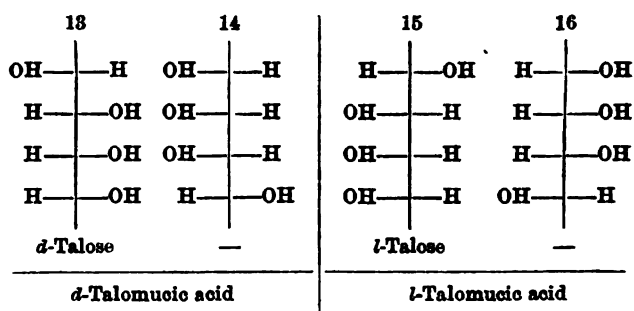
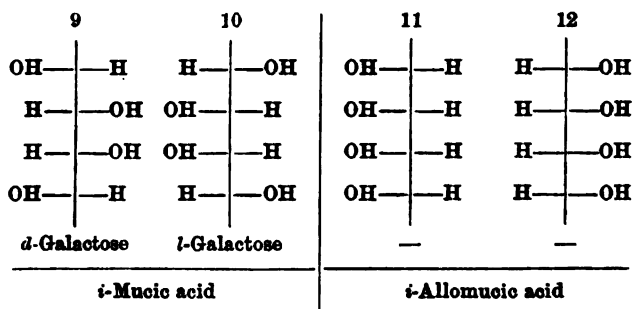


Each pentose will furnish two hexoses, making altogether sixteen stereoisomers. They may for convenience be divided into two groups of eight, known respectively as the mannitol and dulcitol group. In appending the names in the following table, we have anticipated the discussion of their configuration with the object of economizing space. The names of the dibasic acids are placed below the sugar or sugars from which they are derived for purposes of reference. It will be noticed that in the mannitol group the middle pair of asymmetric groups are diagonally situated ; in the dulcitol group they are symmetrically arranged.

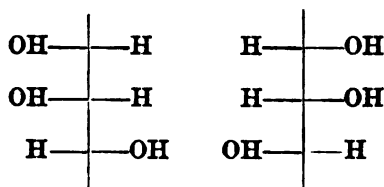
Mannitol Group.



THE CARBOHYDRATES

*Dulcitol Group.*

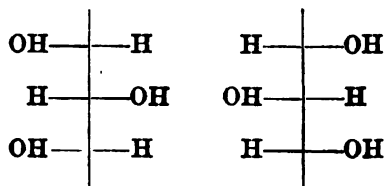
The configurations of the pentoses furnish a basis for that of the hexoses. As *d*- and *l*-glucose can be converted by Wohl's method into *d*- and *l*-arabinose, the configurations of the three upper asymmetric carbon atoms of the glucoses is given.



d-, *l*-Arabinose.

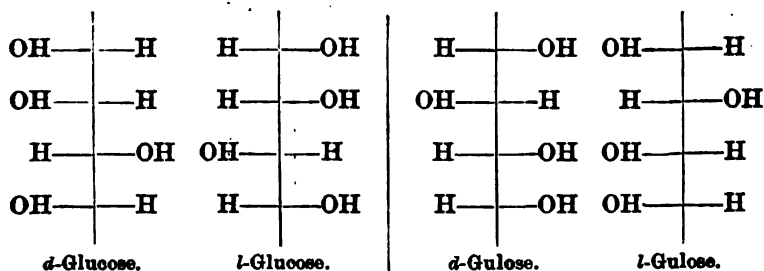
The same partial structure must be assigned to the mannoses, seeing that *l*-arabinose has been transformed into a mixture of *l*-mannose and *l*-glucose (p. 815).

For similar reasons the idoses and guloses are related to *d*- and *l*-xylose and consequently contain the grouping :



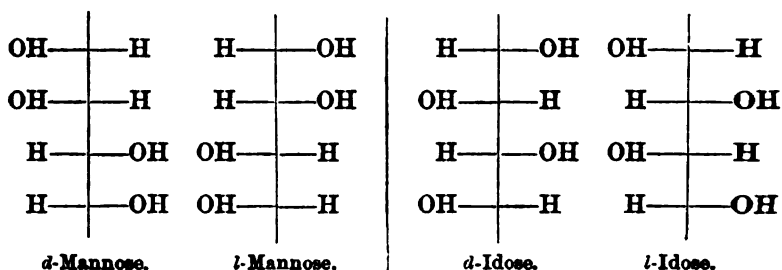
d-, *l*-Xylose.

Now, as the guloses are obtained from the glucoses by inversion of aldehyde and primary carbinol groups, the three upper asymmetric groups in gulose will represent the three lower asymmetric groups in glucose. Consequently, by combining the xylose and arabinose formulae we obtain the glucoses and the guloses.

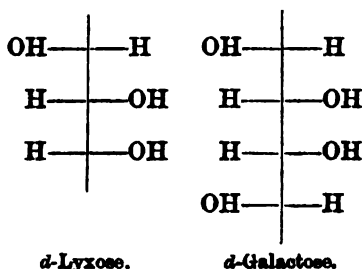


The first formula is arbitrarily assigned to *d*-glucose and the others consequently follow. The configuration of the upper three carbon atoms will also enable similar distinctions to be drawn between the dextro and laevo enantiomorphs of arabinose and xylose. As both *l*-glucose and *l*-mannose are obtained by the cyanhydrin synthesis from *l*-arabinose, as moreover they both yield the same osazone, and as mannonic acid is partly converted into gluconic acid by inversion, the only

difference in their configurations must relate to the bottom asymmetric carbon atom. The same difference exists between the idoses and guloses. The mannoses and idoses will consequently have the following structure :



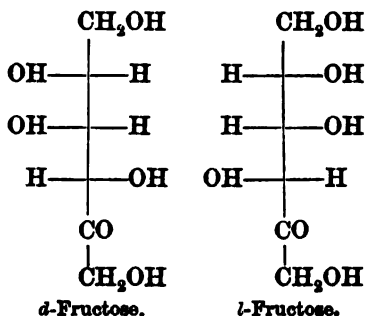
The above configurations are confirmed by the following observations. It will be seen on reference to the eight configurations of the mannitol group (p. 319) that, whilst each of the first four should yield a different saccharic acid on oxidation, the second four require only one saccharic acid for each pair of stereoisomers, and this strictly theoretical deduction stands in complete harmony with the facts. The configurations of the galactoses and taloses are determined as follows : as the galactoses give on oxidation the same inactive, or meso-mucic acid, their configuration is limited to the first two pairs of stereoisomers (9-12) of the dulcitol group. But *d*-galactose has been transformed into *d*-lyxose, and the latter can only differ from xylose in the configurations of the bottom asymmetric group. Consequently lyxose and galactose will have the following configurations :



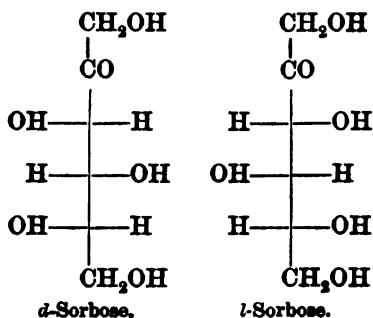
As *d*- and *l*-talose are obtained by inversion from *d*- and *l*-galactose, the configuration of the last two members of the hexose group is known.

Configuration of the Keto-Hexoses. The configuration of the aldo-hexoses being known, that of the keto-hexoses is readily ascer-

tained. Thus *d*-glucose has been transformed into *d*-fructose, and they both yield the same glucosazone. It follows that the three asymmetric groups of *d*-fructose and *d*-glucose are identical.

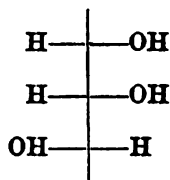


As *d*-sorbosc is obtained by oxidising *d*-sorbitol, which is the alcohol corresponding to *d*-glucose, the configuration of the three lower asymmetric groups in *d*-sorbosc must be that of *d*-glucose.



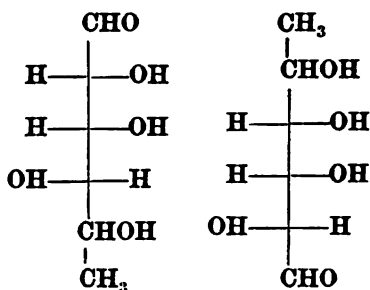
This is confirmed by the identity of the osazone of *l*-sorbosc (*ψ*-tagatose) with those of *l*-gulose and *l*-idose.

Configuration of the Rhamnose group. Rhamnose gives, on oxidation, the same *l*-trihydroxyglutaric acid as that derived from *l*-arabinose. It therefore contains the complex :

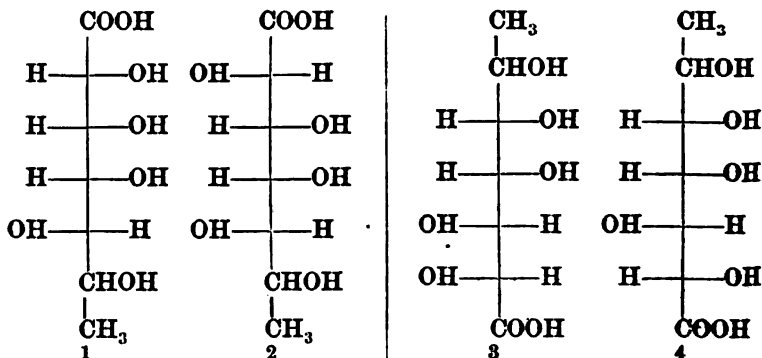


Rhamnose is therefore represented by one of the following forms, on

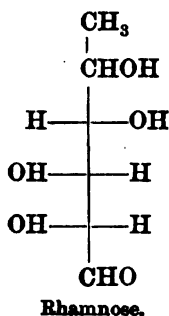
the assumption that the methyl group is removed, and the remaining two end groups converted into carboxyl:



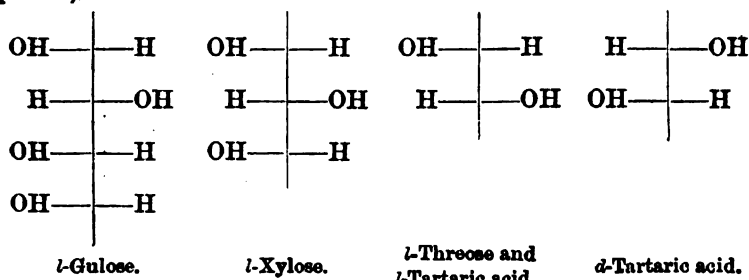
Now rhamnose yields by the cyanhydrin reaction two, α - and β -, rhamnohexonic acids, one of which gives mucic and the other *l*-talomucic acid on oxidation. The rhamnohexonic acids will consequently be represented by two of the following pairs of configurations, one being derived from the first and the other from the second of the above formulae for rhamnose.



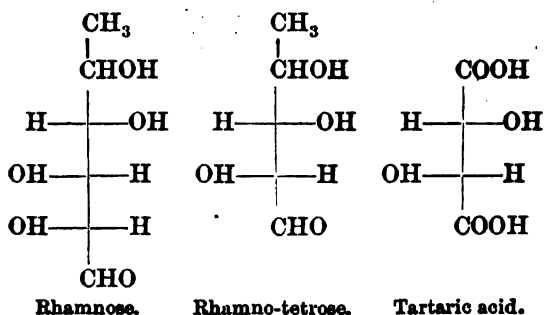
It is obvious that the rhamnohexonic acids cannot be represented by 3 and 4, since the configuration of these two compounds belongs to members of the mannitol group which are already known. Therefore, as mucic acid is an inactive meso compound, the rhamnohexonic acid corresponding will be represented by 2, whilst the second rhamnohexonic acid which gives *l*-talomucic acid has the configuration 1. Rhamnose is therefore represented by the first of the two configurations given above, the proof of which incidentally determines that of galactose and *l*-talose (which correspond to mucic and *l*-talomucic acid) and partially that of the other rhamnose derivatives.



Relative Configuration of the Tartaric Acids. The relation of the *d*- and *l*-tartaric acids to the glucoses can be readily ascertained through *l*-threose, which, on the one hand, gives *l*-tartaric acid by oxidation, and, on the other, is derived from *l*-xylose and *l*-glucose (p. 308).

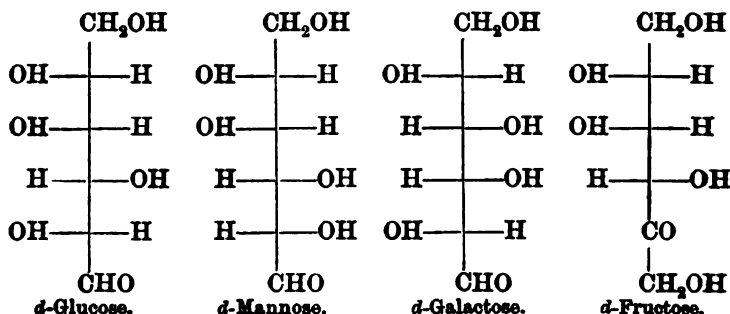


The configuration of *d*-tartaric acid may also be derived from that of rhamnose, since Fischer has shown that rhamnose may be converted by Wohl's method into methyl tetrose, which yields *d*-tartaric acid on oxidation.

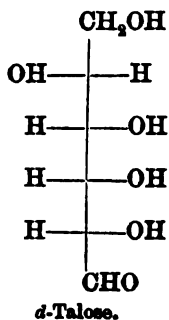


Fermentation of the Monosaccharoses. Pasteur was the first to show that a solution of racemic acid becomes laevo-rotatory in presence of *penicillium*, owing to the destruction of the dextro-

tartaric acid by the fungus—an observation which has been frequently utilized in the attempt to isolate one of the optical enantiomorphs from an inactive mixture (p. 76). Fischer has shown that this selective action is exhibited in a very marked degree by the beer yeasts in producing fermentation of carbohydrates. Of the twelve known aldo-hexoses only the three natural sugars are fermentable, viz., *d*-glucose, *d*-mannose, and *d*-galactose, and of the keto-hexoses only *d*-fructose is decomposed. All the yeasts susceptible of inducing fermentation transform *d*-glucose, *d*-mannose, and *d*-fructose, with almost equal velocity, but the action of yeast on *d*-galactose is slower, and certain species—*saccharomyces apiculatus*, and *productivus*—are totally without action upon it. A comparison of the configuration of these four sugars exhibits the differences of molecular grouping.

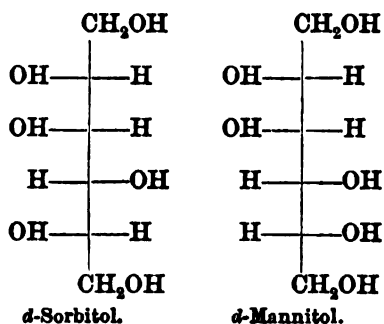
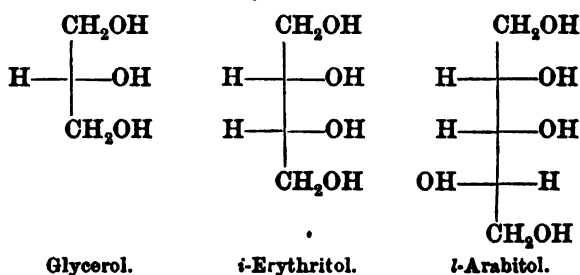


In glucose, mannose, and fructose, the grouping of the H and OH round the three upper asymmetric carbon atoms is the same, but differs from that in galactose, a fact which may account for the slow fermentative action of the latter. The other hexoses are not fermentable. The small difference in configuration which suffices to arrest the action is seen in the case of *d*-talose, which only differs from *d*-galactose by the position of one hydroxyl group.

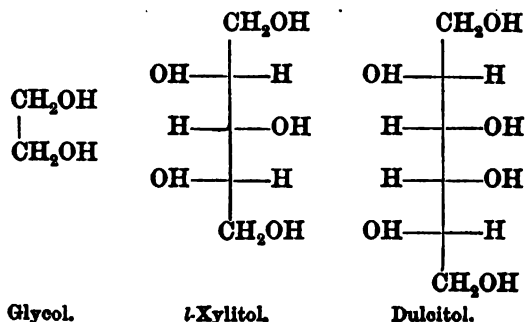


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Of the other monosaccharoses only glycerose and manno-nonose, that is, sugars with three, or a multiple of three, carbon atoms are known to undergo fermentation. This curious selective action of the organism is repeated in the case of the polyhydric alcohols. Bertrand,¹ in his brilliant investigation on the sorbose bacterium, has shown that the conversion of the alcohols into ketoses is dependent on their configuration, and that whereas glycerol, *m*-erythritol, *l*-arabitol, *d*-sorbitol, *d*-mannitol, &c., with the following configurations, are oxidised by the bacterium,



glycol, *l*-xylitol, and dulcitol are not.

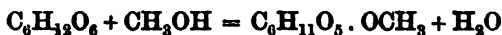


¹ *Ann. Chim. Phys.*, 1904 (8), 3, 181.

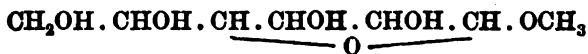
A comparison of the two series indicates that the difference of configuration is confined to the two upper asymmetric carbon atoms, and the conclusion seems inevitable that it is the difference of configuration which determines decomposition by the organism. To explain this selective action, Fischer introduced the simile of a lock and key. That the organism has an asymmetric structure seems manifest from the optical activity of protein matter, and when this structure corresponds to that of the organic molecule, or the wards of the key fit those of the lock, decomposition can occur. The subject is more fully considered under 'Fermentation' (p. 837).

Constitution of the Disaccharoses. Our knowledge of the natural disaccharoses, in spite of few successful syntheses, is fairly complete. It seems certain that these compounds possess the constitution of ethers in the sense that the carbon groups of two or more simple sugars are linked by oxygen. This is the view held by Fischer, who prepared a number of compounds of the monosaccharoses with alcohols by the action of hydrochloric acid upon a mixture of the sugar and the alcohol.

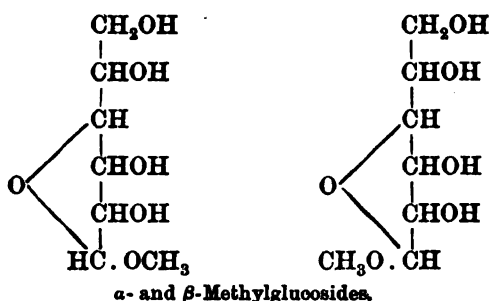
These products, like the polysaccharoses and glucosides, undergo hydrolysis by contact with enzymes, or by boiling with dilute acids (p. 299). Thus, the substance which Fischer terms methyl glucoside is obtained by the action of hydrochloric acid in the cold, upon a mixture of glucose and methyl alcohol.



As the new compound has forfeited its aldehydic properties, Fischer explains its structure by the following formula:



If this is the correct explanation, the formation of the methyl glucoside must be accompanied by the creation of a new asymmetric carbon atom (indicated in thick type) and consequently of two stereoisomers, in the same manner that two cyanhydrins are formed by the addition of hydrogen cyanide (p. 302). This is precisely what occurs, and in the majority of cases two stereoisomers, distinguished as α and β , have been isolated. The structure of the α - and β -methylglucosides may be represented in the following manner:



The following is a list of aldoses and ketoses obtained in this way:

<i>Aldosides.</i>	
<i>α</i> -Methyl <i>d</i> -glucoside	Methyl <i>d</i> -mannoside
<i>β</i> -Methyl <i>d</i> -glucoside	Methyl <i>l</i> -mannoside
<i>α</i> -Methyl <i>l</i> -glucoside	Methyl rhamnoside
<i>β</i> -Methyl <i>l</i> -glucoside	Ethyl rhamnoside
<i>α</i> -Methyl <i>dl</i> -glucoside	Methyl arabinoside
<i>α</i> -Ethyl <i>d</i> -glucoside	Ethyl arabinoside
Propyl <i>d</i> -glucoside	Benzyl arabinoside
Phenyl <i>d</i> -glucoside	<i>α</i> -Methyl xyloside
Benzyl <i>d</i> -glucoside	<i>β</i> -Methyl xyloside
<i>α</i> -Methyl <i>d</i> -galactoside	Methyl gluco-heptoside
<i>β</i> -Methyl <i>d</i> -galactoside	<i>Ketosides.</i>
Ethyl <i>d</i> -galactoside	Methyl sorboside
	Methyl fructoside

What has been said of the selective action of yeast and the sorbose bacterium applies to that of enzymes on the artificial alkyl glucosides. Fischer¹ made the interesting observation that an aqueous extract of pulverized yeast cells, which contains an enzyme *maltase*, hydrolyses *α*-methyl *d*-glucoside, but has not the least action on the *β*-methyl *d*-glucoside. Exactly the reverse happens with the emulsin of bitter almonds which hydrolyses the *β*-glucoside, whilst the *α* modification remains unchanged. The ethyl and phenyl glucosides, of each of which only one modification is known, behave like the *α*-methyl compound, and probably belong to the same category. Similar differences have been observed in the case of other glucosides both natural and artificial; in other cases again neither enzyme has any action.

The following is a list of natural and artificial glucosides. The

¹ *Zeit. physiol. Chem.*, 1898, 26, 61.

action of the enzyme is denoted by + when it produces hydrolysis and by - when it is without action.

Artificial glucosides.	Emulsin.	Maltase.
α -methyl <i>d</i> -glucoside	-	+
β -methyl <i>d</i> -glucoside	+	-
α -methyl <i>l</i> -glucoside	-	-
β -methyl <i>l</i> -glucoside	-	-
α -ethyl <i>d</i> -glucoside	-	+
phenyl <i>d</i> -glucoside	+	-
α -methyl <i>d</i> -galactoside	-	+
β -methyl <i>d</i> -galactoside	+	-
methyl <i>d</i> -mannoside	-	-
methyl <i>l</i> -mannoside	-	-
methyl arabinoside	-	-
α -methyl xyloside	-	-
β -methyl xyloside	-	-
methyl rhamnoside	-	-
methyl gluco-heptoside	-	-
methyl sorboside	-	-
methyl fructoside	-	+

Natural glucosides.	Emulsin.	Maltase.
Salicin	+	-
Helicin	+	-
Aesculin	+	-
Coniferin	+	-
Phillyrin	-	-
Aprin	-	-
Syringin	+	-
Saponin	-	-
Phloridzin	-	-
Mandelo nitrile glucoside	+	-
Amygdalin	+	+
Quercitrin	-	-

It would appear that the majority of the natural glucosides belong to the group of β -glucosides.

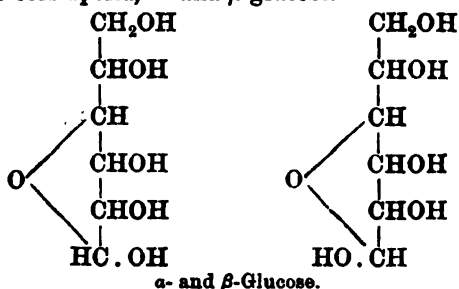
We shall see presently that the disaccharoses are subject to the same selective hydrolysis by enzymes and are divisible into two stereochemically related groups.

Structure of Glucose as determined by Enzyme Action. The above observations on enzyme action will enable us to understand a new theory of the structure of glucose and the other monosaccharoses which has been incidentally referred to on p. 296. It has already been stated that many of the sugars are subject to mutarotation (p. 100), that is, to a change in rotation when the freshly prepared solution of the substance is allowed to stand, or, more quickly, if a trace of alkali is added and the liquid warmed. Thus, *d*-glucose freshly dissolved in water exhibits a rotation of $[\alpha]_D = +105^\circ$, which becomes constant when it has dropped to half, i.e. $[\alpha]_D = +52.5^\circ$.

The change has been variously ascribed to hydration and to change of structure. Both the modifications known as α - and β -glucose and an additional γ -glucose having a rotation $[\alpha]_D = +22^\circ$ have been isolated by Tanret.¹ The first two were prepared by crystallization of glucose from the cold and hot solutions respectively, and the last from its solution in alcohol at a high temperature. Whichever of the three modifications is dissolved, the rotation becomes constant when $[\alpha]_D = +52.5^\circ$. It appeared, therefore, not improbable that the intermediate β -glucose represented a mixture of dynamic isomers. Simon² was the first to suggest that α - and γ -glucose correspond to α - and β -methyl glucoside, since the mean values of the sum of the rotations are nearly the same :

α -methyl glucoside	+ 157°	α -glucose	+ 105°
β - " "	- 82	γ - " "	+ 22
	+ 125		+ 127
mean = + 62.25		mean = + 68.5	

If this is the case, α -methyl glucoside, on hydrolysis, should yield a sugar of high, β -methyl glucoside of low rotatory power. The glucoses themselves are, however, so sensitive to ordinary chemical reagents that hydrolysis of the glucosides by acids or alkalis is precluded. E. F. Armstrong³ hit upon the ingenious device of hydrolysing the glucosides by the aid of the enzymes, emulsin and maltase, and determining the rise or fall of rotation when equilibrium was reached, a process which can be quickly effected by adding a trace of alkali to the resulting solution. Small but definite indications of the existence of two glucoses were obtained, which must consequently be represented by configurations similar to the α - and β -glucosides and named to correspond, α - and β -glucose.



The lactone structure of the glucoses is supported by many independent facts, notably the evidence derived from observations of the magnetic rotation.⁴

Lowry⁵ has discussed at some length the mechanism of the

¹ *Compt. rend.*, 1895, 120, 1060.

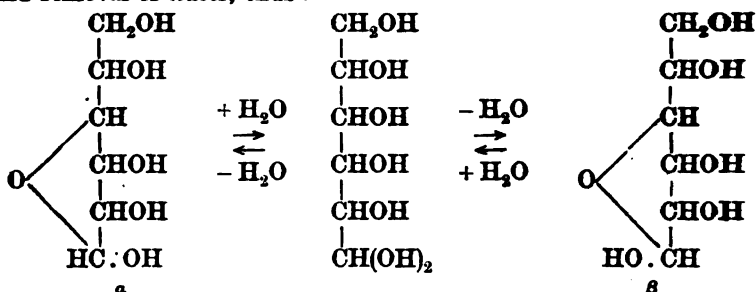
² *Compt. rend.*, 1901, 132, 487.

³ *Trans. Chem. Soc.*, 1908, 85, 1806.

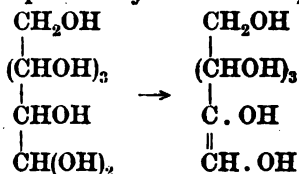
⁴ Perkin, *Trans. Chem. Soc.*, 1902, 81, 177.

⁵ *Trans. Chem. Soc.*, 1908, 85, 1814.

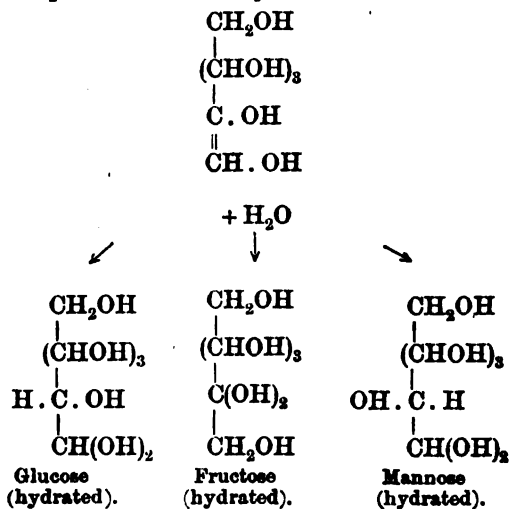
isomeric change by which the two sugars are formed, which he regards as a reversible process effected by the successive addition and removal of water, thus :



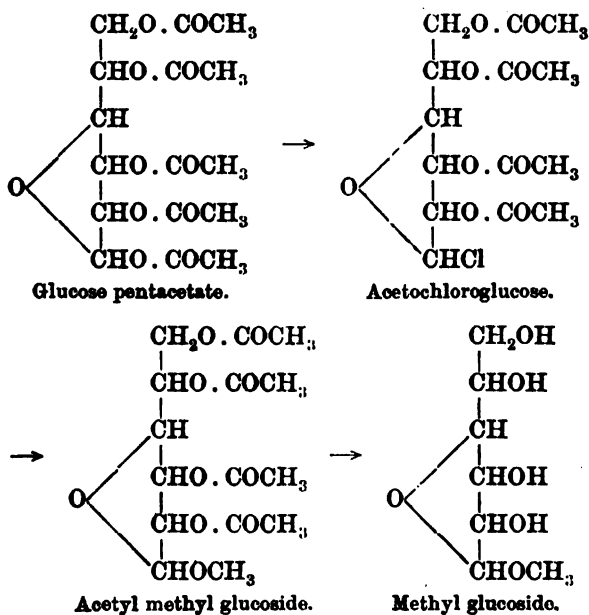
The existence of the above intermediate compound may also explain the interconversion, under the influence of alkalis, of glucose, mannose, and fructose, observed by Lobry de Bruyn and van Ekenstein and already referred to on p. 305. Lowry has suggested that the compounds in question may have a common enolic form, derived from the intermediate product by loss of water, thus :



The production of glucose, mannose, and fructose can be represented as a hydration process followed by lactone or ketone formation, thus :



In addition to α - and β -methyl glucoside, there are many other derivatives of α - and β -glucose. It has long been known that a different glucose acetate is formed by the use of acetic anhydride and zinc chloride, or acetic anhydride and sodium acetate, according to the method of preparation.¹ These have now been brought into relation with the two methyl glucosides by a method devised by Koenigs, and successfully applied by Fischer and Armstrong.² It consists in converting the pentacetates of glucose, by means of liquid hydrogen chloride, into the α - and β -acetochloroglucoses, the chlorine in the latter being then replaced by methoxyl by the combined action of methyl iodide and silver carbonate. The acetyl methyl glucosides are then hydrolysed to remove the acetyl groups.



The α -acetochloroglucose is very rapidly converted into the β -compound by the addition of a little sodium carbonate.

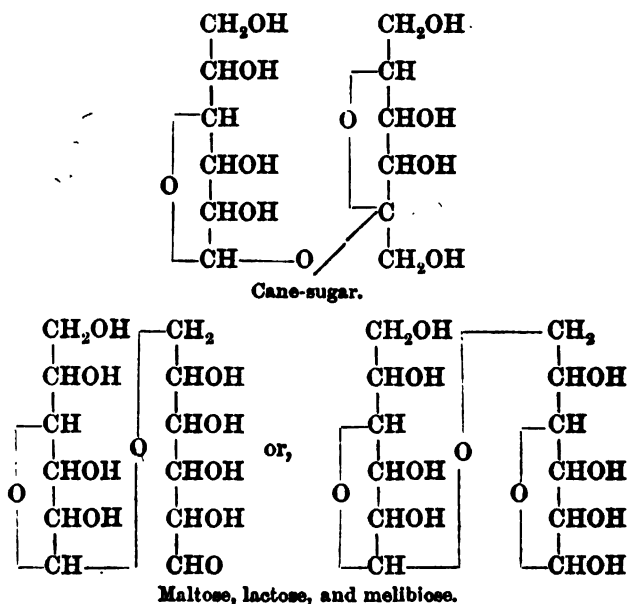
Structure of the Disaccharoses. If the disaccharoses are structurally related to the alkyl glucosides, that is, if they are ether combinations of one hexose with another, they should exhibit similar properties; in other words, they should exist in two stereoisomeric

¹ Erwig and Königs, *Ber.*, 1889, 22, 1464; Franchimont, *Rec. trav. Pays. Bas*, 1892, 11, 106.

² *Ber.*, 1901, 34, 2385.

forms corresponding to α - and β -glucosides, capable of differentiation by enzyme action. Furthermore, it might be anticipated that their synthesis would be effected by the method used in the preparation of the glucosides. Each of these deductions has been in turn verified by Fischer and his collaborators. By the action of hydrochloric acid upon glucose in the cold, Fischer¹ obtained a disaccharose very similar to maltose, but unlike the latter, amorphous and non-fermentable by yeast. It was named *isomaltose*.

The relation of the disaccharoses to the α - and β -glucosides has been established by E. F. Armstrong² by the same method which he applied to α - and β -glucose, namely, by observing the rise or fall of rotation of the glucose isolated by the enzyme, when equilibrium was established. Using maltase and invertase as hydrolysing enzymes, it was shown that maltose and cane-sugar are α -glucosides, raffinose is an α -glucoside of melibiose, whilst starch, which is hydrolysed by diastase, appears to be a β -maltoide. Fischer has assigned the following structural formulae to the disaccharoses, cane-sugar (sucrose), milk-sugar (lactose), malt-sugar (maltose) and melibiose.



The formulae are based partly on the relation of the disaccharoses to the alkyl glucosides, partly on the general chemical behaviour of the sugars themselves. Thus, cane-sugar has no reducing properties and

¹ *Ber.*, 1890, 23, 3688.

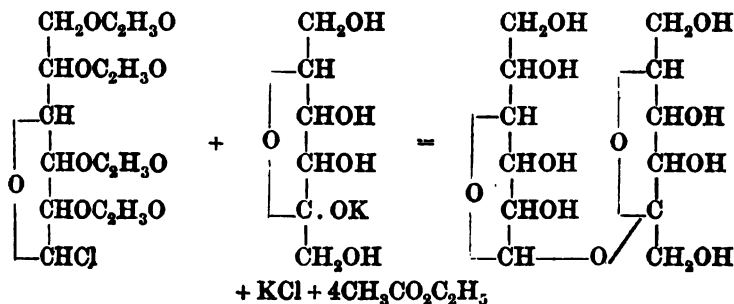
² *Trans. Chem. Soc.*, 1908, 85, 1905.

forms neither hydrazone nor osazone, whereas maltose, lactose, and melibiose behave in this respect like the aldo-hexoses. The difference between maltose, lactose, and melibiose is determined by the space configuration of the individual hexoses which are united in the molecule. The formula does not, however, indicate which half of the molecule in lactose and melibiose represents glucose and which galactose. Fischer and Armstrong¹ have found a simple way of solving the problem by forming the osone of the disaccharose and then hydrolysing it; the resulting hexosone will be that of the aldose constituent. Thus lactose appears to be a glucosido-galactose and melibiose a galactosido-glucose. The structure of melibiose has also been determined synthetically.

Synthesis of the Disaccharoses. The first synthetic disaccharose was obtained, as we have seen, by the action of hydrochloric acid on glucose, and although the method was used successfully in preparing a variety of phenol glucosides, when applied to the disaccharoses it proved to be unsatisfactory. Many years before, another process had been indicated by Michael,² who in 1881 obtained a phenolglucoside by the interaction of acetochloroglucose and potassium phenol in alcoholic solution.



The synthesis of cane-sugar by Marchlewski³ in 1899 was based upon this method. Potassium fructosate and acetochloroglucose, dissolved in alcohol, were allowed to stand for a week, when cane-sugar, potassium chloride, and ethyl acetate were found to have been formed, the reaction probably taking place according to the equation:



The new method devised by Fischer⁴ in 1902 for the preparation of the acetochlorohexoses, by the action of liquid hydrogen chloride on

¹ Ber., 1902, 35, 3141.

² Ber., 1881, 14, 2097.

³ Trans. Acad. Sciences, Cracow, 1899.

⁴ Ber., 1902, 35, 883, 3144, 3153.

the penta-acetates (p. 383), enabled him to apply Michael's reaction to effect the union of a variety of hexoses. By combining acetochloroglucose with sodium galactose, acetochlorogalactose with sodium glucose, and acetochlorogalactose with sodium galactose, three synthetic disaccharoses were created, all of which are hydrolysable by emulsin, whilst the second of the series, galactosido-glucose, is fermented by yeast and is probably identical with melibiose.

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Kurzes Handbuch der Kohlenhydrate, 2 vols., by B. Tollens. Trewendt, Breslau, 1888 and 1895.

Chemie der Zuckerarten, by E. O. von Lippmann. Vieweg, Brunswick, 1895.

CHAPTER IX

FERMENTATION AND ENZYME ACTION

FERMENTATION may be broadly described as a process by which certain products are elaborated as the result of the activity of living cells. The lifeless products of the cells which directly induce these changes are termed *enzymes*, and act either in the presence or absence of the living organism. Fermentation is therefore a result of which enzymes are the active cause.

Thus, the original meaning of the word, which was derived from *fervere*, to boil, and which connected it with the evolution of gas, has entirely disappeared.

Historical. The early history of fermentation is mainly concerned with alcoholic fermentation. Until the sixteenth century it was commonly supposed that the alcohol was present before fermentation in combination with impurities, which were removed during the process, thus liberating the alcohol. In 1682 Becher proved that sugar was necessary for fermentation and that the alcohol did not pre-exist in the liquid. Towards the close of the eighteenth century Lavoisier demonstrated the true composition of cane-sugar, estimated its constituents, and followed quantitatively its conversion into alcohol and carbon dioxide. In 1837 an important advance was made by Cagniard de la Tour in France, and almost simultaneously by Schwann and by Kützing in Germany. They observed under the microscope the reproduction, by budding, of the small spherical bodies which had been seen many years previously by Leuwenhoek in the sediment or scum of fermenting liquids. They associated the disappearance of the sugar and the production of alcohol and carbon dioxide with the presence and reproduction of the organism. Notwithstanding the convincing nature of their experiments it was not until a quarter of a century later (1860) that the dependence of fermentation on the vegetative function of the yeast cell was generally accepted. The *vitalistic theory*, as it was called, had to contend against the strenuous opposition of Liebig and others of his school, who strove to explain the phenomena of life by the aid

of purely chemical and physical laws. Instead of crediting the yeast organism with the power of causing fermentation, they constructed a mechanical hypothesis, known as the *physical* or *vibration theory*. According to this hypothesis the real ferment was a non-living substance which rapidly decomposed, and in so doing transmitted a shock to the sugar molecules by which they were resolved into simpler substances. The theory was in fact a revival of the old views of Willis and of Stahl, which were put forward during the latter half of the seventeenth century. It was not long before a modification of Liebig's original conception was found necessary. The brilliant and conclusive researches of Pasteur left no doubt that the active agent in the change was the living cell. Efforts were made to bring the two views into harmony, and Naegeli put forward the theory that all substances capable of fermentation have their molecules in a state of active oscillation in virtue of their potential energy. The ferment, being in a similar condition, transmitted its motion to the fermenting material outside the living cell and thus effected its decomposition. The ferment itself was not supposed to be destroyed in the process, as Liebig had postulated in his original hypothesis.

At length, after nearly twenty years of fruitless discussion, Pasteur was able to definitely prove that alcoholic fermentation was essentially an intracellular change effected by living yeast, and to show that the lactic and butyric fermentations were kindred phenomena caused by individual organisms distinct from the yeast plant.

Meaning of Fermentation. Until comparatively recently a more or less sharp line of demarcation was drawn between a change, such as fermentation by yeast, and those reactions which are brought about by substances to which the name *enzyme* has been given. Emulsin, an enzyme found in bitter almonds, was observed as early as 1830 by Robiquet and Boutron, and its mode of action was elucidated in a striking way by Liebig and Wöhler.¹ They showed that the enzyme occurred along with the glucoside, *amygdalin*, and that when the cells of the almond are ruptured in the presence of water the two substances are brought into contact, with the result that the glucoside is resolved into benzaldehyde, hydrocyanic acid, and glucose.

By suitable methods it is possible to separate the enzyme from the glucoside and from the cells of the almond, and the reaction may consequently be carried out under conditions which preclude the possibility of any living material being concerned in the change.

¹ *Ann. Chim. Phys.*, 1837, 64, 185.

A similar reaction had been observed as far back as 1814 by Kirchhoff, who discovered the conversion of starch into sugar by the presence of a watery extract of germinating barley, and twenty years later Payen and Persoz were able to roughly isolate the enzyme, to which they gave the name *diastase*. A similar enzyme was also discovered in the salivary secretion by Leuchs, and about the same time *pepsin*, an enzyme which brings about the hydrolysis of proteins, was found by Schwann in the gastric juice.¹

Ferment reactions were therefore divided into two classes—reactions induced by *organised ferments* connected with the presence of living cells, and those caused by *unorganised ferments* capable of acting in a sterile medium.

This distinction persisted for a long time, although suggestions had been made that the difference between the two kinds of change was more apparent than real.² In 1896 E. Buchner was able to show that by rupturing yeast cells by mechanical means and expressing the cell juice under high pressure, a liquid is obtained which is capable of converting a not inconsiderable amount of sugar into alcohol and carbon dioxide in the complete absence of living yeast cells. This result at once placed alcoholic fermentation—the fermentation *par excellence*—upon a level with the changes produced by unorganised ferments. Further research has shown that by similar methods other organisms, particularly those which cause the lactic and acetic fermentations, may be made to yield crude enzyme preparations which are free from living cells, but are still capable of inducing the particular change associated with the organism from which they were derived.

The tendency is therefore to ascribe fermentation reactions, whether associated with living cells or not, to the structureless, non-living enzymes, although it must be admitted that many fermentations are known which cannot at present be shown to take place in the absence of living matter. It is therefore better to designate ferments as *intracellular* or *extracellular* according as they normally operate within or without the cell by which they are formed, not forgetting that in very many cases it is possible by artificial means to cause intracellular enzymes to exert their functions independently of the cell.

¹ The discovery of the ferments concerned in gastric digestion must really be ascribed to Réaumur (1752) and the Abbé Spallanzani (1785). The latter caused birds of prey to swallow small sponges attached to a string. After withdrawal, the sponges yielded a small quantity of gastric juice which was able to dissolve and change fragments of meat. These results were, however, not accepted as correct until many years later.

² Moritz Traube, *Pogg. Annalen*, 1858, 103, 331.

Enzymes are substances of the utmost importance to all living matter. They may be regarded as the 'chemical reagents' of the organism. Their presence, even in minute quantities, effects the disintegration of large amounts of complicated substances of the most varied kind into simpler bodies, which are disposed of or utilized according to the requirements of the cell. They also furnish the means whereby the sun's energy, through the medium of plant life, is made available for the animal organism.

Fermentation, a Catalytic Process. The similarity existing between enzyme actions and ordinary catalytic or contact changes had not escaped the notice of Berzelius. The view of Ostwald that catalysis is essentially an increase in the velocity of a reaction, which normally proceeds at a definite though extremely small rate in the absence of a foreign substance or catalyst, is quite in harmony with all that is known of enzymes. Like most catalytic processes, the speed of fermentation increases with the amount of enzyme. Another and striking analogy between inorganic catalysts and enzymes is the reversibility of certain ferment actions. The recent work which has been carried out upon both inorganic and organic catalysts, by the application of physical methods to the measurement of reaction velocities, has only served to emphasize their close connection. The mechanism of enzyme action is briefly discussed on p. 368.¹

Chemical Action of Enzymes. The majority of enzyme reactions are of a simple hydrolytic character and the energy exchanges are small (e.g. the saponification of fat, the conversion of starch into sugars, the liberation of sugars from glucosides), and most of them can be carried out equally well with inorganic catalysts such as acid or alkali. Even some of the more complicated ferment changes, such as the oxidation of alcohol to acetic acid and the conversion of calcium formate into hydrogen, carbonic acid and calcium carbonate, may be effected by finely divided metals such as platinum and iridium. It must, however, be remembered that, unlike most of the inorganic catalysts, the enzymes are to a considerable extent 'specific', e.g. a fat-hydrolysing enzyme is incapable of hydrolysing starch or glucosides. There is a large amount of

¹ Asher and Spiro, *Ergebnisse der Physiologie*, 1908, 1, 134; Bredig, *Anorganische Fermente*, *Habilitationschrift*, Leipzig, 1904; Victor Henri, *Les Lois Générales de l'Action des Diastases*, Paris, A. Hermann, 1908; Senter, *Proc. Royal Soc.*, 1906, 74, 201; Euler, *Zeit. physiol. Chem.*, 1906, 45, 420.

indirect evidence to support the view that an enzyme enters into a *definite combination* with the substance which undergoes change.

It is usually assumed, from analogy with other catalysts, that a minimum quantity of enzyme is capable of causing the decomposition of an infinitely large amount of the substance upon which it acts, provided that the necessary time is allowed. Practically, however, this condition of things is seldom approached, although in a few cases—notably the action of invertase upon cane-sugar and of the clotting enzyme, rennet—the enzyme is capable of bringing about change in more than one hundred thousand times its own weight of substance without losing its activity. It is, however, much more usual for a considerable destruction of the enzyme to take place during the reaction, and it is a significant fact that the conditions most favourable to the rapid action of many enzymes are precisely those which promote their destruction. For example, the protein-dissolving enzyme, trypsin, secreted by the pancreas, acts most readily at a moderately high temperature and in a comparatively strong alkaline medium, and under these conditions the enzyme is rapidly destroyed, particularly in the absence of protein upon which it may act. In other cases the products formed during the reaction act prejudicially. Thus, the free acid, liberated from fats by animal lipase, has a distinctly harmful effect upon the enzyme. It follows that there is a definite limit to the amount of change that a certain quantity of enzyme can bring about; but the fact is not necessarily opposed to the action being catalytic.

Composition of Enzymes. It has not been possible to isolate an enzyme in the pure state, and up to the present it has been impracticable to do more than investigate the effects produced when mixtures containing them are allowed to act upon substances of known composition. Of the enzymes themselves we know extremely little. In many cases it is possible to obtain solid amorphous preparations, which furnish extremely active enzyme solutions when dissolved in water. Unfortunately there is no definite criterion of purity to serve as a guide, and the methods available for the preparation of enzymes are such as would not remove many known impurities. As a rule enzymes are thrown out of solution on addition of alcohol or salts, such as ammonium or sodium sulphates. Frequently they may be carried down with neutral precipitates, such as calcium phosphate, when formed in their presence. The precipitation of an alkaline solution of a protein, such as casein, with a weak acid, is often effective. In some cases, particularly that of the protein-hydrolysing enzymes, they

may be withdrawn from solution by shaking with insoluble substances such as blood-fibrin, charcoal, cholesterin, or magnesium carbonate.

Generally speaking it is found that the most carefully purified enzyme preparations give the reactions of proteins, and for a long time the view was prevalent that enzymes belonged to the class of nucleo-proteides (p. 421). It is certain, however, that many enzymes are known which are not nucleo-proteides, and some, such as the vegetable oxidases, seem to contain scarcely any nitrogen.¹ The general properties of enzymes lead to the conclusion that they are unstable substances of very high molecular weight, and there are good reasons for believing that their molecules are asymmetric. They appear to be colloidal substances, as they are practically non-dialysable. In solution they are almost all destroyed at temperatures of about 65–85°, but in the absence of water they are more stable, and some have been heated to 150° without losing their activity.

It is probable that the enzymes will be found to be allied to the class of substances upon which they act. The enzymes which act upon the xanthine bases are intimately connected with nucleo-proteides, which themselves furnish xanthine bases upon hydrolysis. The purest pepsin yet obtained was found by Pekelharing² to have an elementary composition not differing widely from most proteins (C = 52, H = 7, N = 14.8, S = 1.65) and to resemble the nucleo-proteides in some other particulars. Trypsin, papaIn, and thrombase, all enzymes which act upon protein substances, would also appear to resemble complex protein derivatives, and this view is supported by the fact that the three proteases, trypsin, pepsin, and papaIn, are able to mutually 'digest' one another. According to O'Sullivan and Thompson,³ invertase contains a carbohydrate, possibly in combination with a protein. Diastase,⁴ however, appears to be a protein derivative.

Enzyme preparations invariably contain small quantities of inorganic matter, which in some cases seems to be of great importance. A striking example of this is seen in 'laccase', an oxidising enzyme

¹ The difficulties attending the satisfactory isolation of enzymes has led some investigators to doubt their real existence as definite substances. Arthus (*La Nature des Enzymes*, Thèse, Paris, 1896) expresses the view that enzymes represent no material substances, but are forms of imponderable energy comparable with light, electricity, &c. Others have tried to draw analogies between the enzymes and the emanations of radio-active substances, but these hypotheses are of course purely speculative, and there are at present no reasons why the older materialistic view should be abandoned.

² *Zeit. physiol. Chem.*, 1902, 35, 8.

³ *Trans. Chem. Soc.*, 1890, 57, 834.

⁴ Wróblewski, *Ber.*, 1898, 31, 1130.

discovered by Yoshida,¹ which plays an important part in the production of lacquer varnish from the sap of the lac tree. Bertrand² finds that the ash contains up to 2 per cent. of manganese, and that the activity of the enzyme is proportional to the manganese present. It was further shown that in certain laccase preparations, which contained an exceptionally low amount of manganese, the action of the enzyme could be increased thirtyfold by addition of manganese salts. It has been suggested that manganese, being able to form compounds of varying degrees of oxidation, acts directly as an oxygen carrier, though salts of other metals cannot replace it. The occurrence of manganese in the ash of tea-leaves is probably connected with the presence of a similar enzyme.

Calcium salts are found to be essential to the action of some of the clotting enzymes, such as rennin and thrombase, whilst chlorine would appear to be a necessary constituent of pepsin. Phosphorus is often found in the numerous enzymes associated with nucleoproteides, though it is not certain that the phosphorus is actually part of the enzyme molecule.

Conditions determining Enzyme Action. Enzymes can act only within a limited range of temperature. Little or no action is observable at the freezing-point, and a temperature of about 60° usually causes a fairly rapid destruction of the ferment, whilst at somewhat higher temperatures their destruction is almost instantly complete. In general, the enzymes of animal origin act best at about blood-temperature (37°), whilst a temperature of about 25° is often favourable for vegetable enzymes. In some cases enzymes from cold-blooded animals seem to act best at a temperature of about 15°.

With few exceptions the enzymes can act only in almost neutral solutions, and in general a faintly acid medium is preferable to one with an alkaline reaction. Trypsin, however, works well in a solution containing 1 to 2 per cent. of sodium carbonate, whilst, on the other hand, pepsin is most active in the presence of 0.2 per cent. of hydrochloric acid. Additions of most foreign substances affect enzyme reactions adversely, but occasionally small quantities of neutral salts are advantageous. Many neutral substances which are very poisonous for the living organism (cyanides, fluorides, chloroform), or aromatic hydrocarbons (toluene, &c.), are not nearly so prejudicial to the enzymes, so that substances of this kind are frequently added to solutions in which enzyme changes are in progress in order to prevent bacterial contamination.

¹ *Trans. Chem. Soc.*, 1883, 43, 472.

² *Compt. rend.*, 1897, 124, 1082.

Specific Action of Enzymes. The simplest reactions brought about by enzymes may be divided into three classes—those which bring about a simple hydrolysis, those concerned in oxidations and reductions (oxidases and reductases), and those which induce clotting of certain substances. The enzymes of the first class may be arranged according to the nature of the substance, or *substrate*, which undergoes change—polysaccharoses, di- and tri-saccharoses, glucosides, proteins and their decomposition products, purine bases, &c.

The nomenclature now in general use for the naming of enzymes is that suggested by Duclaux, and consists in adding the suffix *-ase* to the substance upon which the action of the enzyme was first observed. Certain of the older names, however, such as trypsin and emulsin, &c., are still retained.

Enzymes which induce the hydrolysis of Polysaccharoses.

<i>Enzyme.</i>	<i>Substrate.</i>	<i>Products.</i>	<i>Occurrence.</i> ¹
Diastase (syn. Amylase)	Starch Glycogen	Dextrins Maltose	Veg. { Germinating grain and many plants, fungi, and bacteria Animal { Pancreatic juices, liver, saliva ²
Inulase	Inulin	Fructose	Germinating bulbs and tubers. <i>Aspergillus niger</i>
Cellulase (syn. Cytase)	Cellulose	Reducing sugars	Veg. { Germinating grain, fungi Animal { Livers of carp and snails
Pectinase Gelase	Pectins Gelose	Reducing sugars Reducing sugars	Germinating grain Bact. gelaticus
Caroubinase	(Agar-Agar) Caroubin	Reducing sugars	Carob beans

Amongst the enzymes concerned in the hydrolysis of the polysaccharoses, diastase is by far the most important. It has an extraordinarily wide distribution, the enzymes from both animal and vegetable sources being apparently identical. Relatively pure diastase is easily prepared by extracting green or air-dried malt with dilute spirit, and then precipitating the filtered liquid with absolute alcohol. The crude product is purified by reprecipitation and is freed from most of the inorganic impurities by dialysis. The substance finally obtained is a white powder, of which a very

¹ Only the principal sources of the enzymes can be noted here. A complete account of the distribution would occupy too much space.

² The name 'ptyalin' is commonly given to salivary diastase.

small quantity is able to liquefy a very large amount of starch paste. When allowed to act upon starch paste it is found that after a short time the liquid no longer gives a blue colour with iodine, but a deep red-brown, whilst at a later stage no reaction at all is observable. No definite conclusion as to the nature of the products of the action of diastase upon starch has yet been reached, but it is certain that maltose is the main product. A number of substances belonging to the class of dextrins (erythro-dextrin, achroo-dextrin, amylodextrin, maltodextrin, &c.) have been described by different investigators, but they are difficult to characterize, and much confusion exists as to their individuality.¹ It was formerly believed that iso-maltose was also produced in the reaction, but this view is no longer generally accepted. Vegetable and animal diastase act equally well upon glycogen and upon starch, and the products are similar.

Inulase,² an enzyme occurring in the growing tubers of the artichoke and other plants, is able to bring about the conversion of inulin into fructose, but is without action upon starch. The other enzymes of this group, although of the utmost importance from a biological standpoint, possess little chemical interest, as the nature of the reactions involved is still obscure.

Enzymes inducing the hydrolysis of the Di- and Tri-saccharoses.

<i>Enzyme.</i>	<i>Substrate.</i>	<i>Products.</i>	<i>Principal Occurrence.</i>
Maltase (syn. Glucase)	Maltose	Glucose	Yeast, malt, taka-dia- stase, intestinal juice
Invertase (syn. invertin, sucrase)	Cane-sugar	Fructose, glucose	Yeast extracts, many parts of plants, fungi, intestinal juice
Lactase	Lactose	Glucose, galactose	Kephir organism and some saccharomyces, intestinal juice
Trehalase	Trehalose	Glucose	Penicillium glaucum Aspergillus niger Green malt
Raffinase	Raffinose	Melibiose and fructose	Yeast and Aspergillus niger
Melibiose Melizitase	Melibiose Melizitose	Galactose, glucose Touranose, glucose	Froberg yeast Aspergillus niger
Touranase	Touranose	Glucose	Aspergillus niger

¹ Lintner and Düll, *Ber.*, 1898, 26, 2583; Brown and Morris, *Trans. Chem. Soc.*, 1889, 55, 463; 1895, 69, 709.

² Green, *Annals of Botany*, 1, 223.

Maltase is one of the most important and widely distributed of the enzymes concerned in carbohydrate metabolism. It is found in most varieties of yeast and other fungi, and also in intestinal juice. Its special action is to convert maltose into two molecules of glucose; it is without action upon cane-sugar. Its occurrence along with diastase in malt extracts explains the frequent presence of glucose amongst the degradation products of starch.

Maltose is not directly fermentable by yeast; for it is necessary for the maltase present in the yeast to transform the maltose into glucose before conversion into alcohol and carbonic acid can occur. Since maltase is not readily obtained from yeast, unless the cells are thoroughly dried and then ground with sand and water, it follows that the conversion of maltose into glucose by yeast is an intracellular change.

Similarly it is found that, before maltose can be made use of as a source of energy by the animal organism, it must be first converted into glucose, a change which is brought about by the enzyme present in the intestinal juice.

The action of maltase upon maltose is of special interest, for it has been shown by Croft Hill¹ to be reversible (p. 866). He found that glucose in concentrated solutions under the influence of maltase is partly converted into maltose. The same equilibrium mixture of maltose and glucose is produced whichever sugar is taken as the starting-point, and is dependent upon the concentration of the solutions. With solutions containing less than 4 per cent. of sugar no reversion is observable. Some discussion has taken place as to the exact nature of the sugars formed from glucose. Emmerling² considers that iso-maltose is formed, whereas Croft Hill maintains that maltose and a new disaccharose, *revertose*, are produced, but it is at least certain that a synthetical process has been brought about by the enzyme.

Maltase is also able to bring about the hydrolysis of the α -series of synthetical glucosides obtained by Fischer, to which reference will be made later (p. 848).

Trehalase is an enzyme which converts trehalose into glucose, and in most respects resembles maltase.

Invertase is a comparatively stable enzyme which, when acting under favourable conditions, can convert more than one hundred thousand times its weight of cane-sugar into glucose and fructose. It has no

¹ *Trans. Chem. Soc.*, 1898, 73, 684; 1903, 83, 578.

² *Ber.*, 1901, 34, 600.

action upon maltose and lactose, but apparently can attack gentianose, a complicated sugar which contains a cane-sugar grouping. Invertase appears to play an important part in connection with the photosynthetic production of carbohydrates in green plants. According to Brown and Morris¹ cane-sugar is the first stable carbohydrate formed in the synthesis, and as cane-sugar, like maltose, does not seem to be directly assimilated by the organism, it is converted into the assimilable glucose by means of the invertase, which is commonly found in the green parts of plants.

Invertase is also found in the intestinal juice of most animals, and cane-sugar taken by the mouth is rapidly converted into glucose before absorption. The necessity for this is seen in the fact that cane-sugar, when injected intravenously, is excreted, unchanged, in the urine.

Lactase is the enzyme specially concerned in conversion of lactose into galactose and glucose. It is found in the intestinal juice, and occasionally in the pancreatic secretion of animals. It is much more abundant in young mammals than in adults, but the production of lactase may be induced by continued ingestion of lactose. Its function is similar to maltase and invertase, and, like the former, its action has been shown to be reversible. Fischer and Armstrong,² by acting upon a mixture of galactose and glucose, obtained a disaccharose, isolactose, which is very closely allied to lactose. A disaccharose was also formed when glucose, but not galactose, was present.

Lactase is also found in extracts from the kephir organisms (milk-sugar yeast) and in certain saccharomyces. It is remarkable that it is commonly accompanied by invertase, but seldom if ever by maltase.

The decomposition of raffinose (melitriose) into melibiose and fructose is accomplished by the enzyme *raffinase*. The melibiose may be further hydrolysed by an enzyme—*melibiase*—and yields glucose and galactose. Melibiase may possibly be identical with maltase. A similar hydrolysis of a trisaccharose is met with in the conversion of melizitose into glucose and the disaccharose, *touranose*. The latter sugar is converted into glucose by means of a separate enzyme.

¹ *Trans. Chem. Soc.*, 1898, 63, 604.

² *Ber.*, 1902, 35, 3144.

Enzymes inducing hydrolysis of Glucosides.

<i>Enzyme.</i>	<i>Substrate.</i>	<i>Products.</i>	<i>Principal Occurrence.</i>
Emulsin	Amygdalin ¹	Benzaldehyde, glucose, and hydrocyanic acid	{ Bitter almonds Aspergillus niger Other plants Lotus arabeus
Lotase	Lotusin	Lotoflavin, glucose, and hydrocyanic acid	
Myrosin	Sinigrin (Potassium Myronate)	Allylthiocyanate, potassium hydrogen sulphate, glucose	Cruciferae and other orders
Gaultherase (syn. Betulase)	Gaultherin	Methyl salicylate, glucose	Leaves of Gaultheria procumbens and varieties of Azalea and Spiraea
Indigo ferment (Indimulsin)	Indican	Indoxyl and indiglucein	Indigo plants
Tannase	Tannins	Gallie and ellagic acids, glucose	Aspergillus niger and galls
Rhamnase	Xanthorhamnin	Rhamnetin, rhamnose	Seeds of Persian berry
Erythrozyme	Ruberythric acid	Alizarin and glucose	Madder plant

Enzymes causing hydrolysis of Glucosides. Amongst the hydrolysing enzymes emulsin is by far the most important and the most widely distributed. It has the property of hydrolysing not only amygdalin, as already mentioned, but also a large number of other glucosides, the most important of which are given in the table on p. 849.

Emulsin is also able to act upon certain synthetical glucosides. It will be remembered that by the action of various alcohols upon sugars in the presence of hydrochloric acid, Fischer was able to prepare two series of stereoisomeric glucosides, and that the α -glucosides are exclusively attacked by maltase whereas the β -glucosides are exclusively attacked by emulsin (p. 829).²

It has been possible from these results to draw conclusions as to the configurations of some of the natural sugars and their derivatives. Maltose is clearly to be regarded as an α -glucoside, for it is hydrolysed by maltase and not by emulsin, whilst the observation that emulsin from bitter almonds brings about the hydrolysis of

¹ In many cases an enzyme may cause the hydrolysis of different substances, as in the case of emulsin, which can bring about the decomposition of a whole series of glucosides. In the tables, however, only one typical example can be given.

² Fischer, *Zeit. physiol. Chem.*, 1898, 26, 61.

lactose, and, further, that the enzyme lactase acts upon β -methyl-glucosides, suggests that lactose is related to the β -glucosides.

Alkyl glucosides, derived from non-fermentable sugars such as glucose, the pentoses and heptoses, are unattacked by both enzymes (p. 880).

It appears at first sight a curious anomaly that amygdalin,

<i>Glucoside.</i>	<i>Products of Hydrolysis.</i>
Amygdalin	2 mol. glucose, 1 mol. hydrocyanic acid, 1 mol. benzaldehyde
Mandelo-nitrile glucoside	1 mol. glucose, 1 mol. hydrocyanic acid, 1 mol. benzaldehyde
Coniferin	1 mol. glucose, 1 mol. coniferyl alcohol $\begin{array}{c} \text{OH} \\ \\ \text{C}_6\text{H}_5 \cdot \text{CH} : \text{CH} \cdot \text{CH}_2\text{OH} \\ \\ \text{CH}_2\text{O} \end{array}$
Salicin	1 mol. glucose, 1 mol. saligenin $\begin{array}{c} \text{OH} \\ \\ \text{C}_6\text{H}_4 \\ \\ \text{CH}_2\text{OH} \end{array}$
Arbutin	1 mol. glucose, 1 mol. quinol
Glucovanillin	1 mol. glucose, 1 mol. vanillin $\text{C}_6\text{H}_5(\text{OH}) \cdot (\text{OCH}_3) \cdot \text{C} \begin{array}{l} \text{O} \\ \parallel \\ \text{H} \end{array}$
Helicin	1 mol. glucose, 1 mol. salicylaldehyde
Glucovanillic acid	1 mol. glucose, 1 mol. vanillic acid $\begin{array}{c} \text{HO} \\ \\ \text{C}_6\text{H}_3 \cdot \text{CO}_2\text{H} \\ \\ \text{CH}_2\text{O} \end{array}$
Daphnin	1 mol. glucose, 1 mol. daphnetin $\begin{array}{c} \text{CH} : \text{CH} \\ \quad \\ 8.4.(\text{OH})_2 \cdot \text{C}_6\text{H}_2 \quad \text{O} \quad \text{CO} \end{array}$
Aesculin	1 mol. glucose, 1 mol. aesculetin $\begin{array}{c} \text{CH} : \text{CH} \\ \quad \\ 4.5.(\text{OH})_2 \cdot \text{C}_6\text{H}_2 \quad \text{O} \quad \text{CO} \end{array}$
Phloridzin	1 mol. glucose, 1 mol. phloretin (the phloroglucinol ester of <i>p</i> -hydroxyhydratropic acid)

which from Fischer's early investigations was considered to be a maltoside, and under the influence of maltase was converted into mandelo-nitrile glucoside, should at the same time be attacked by emulsin like a β -glucoside. Bourquelot, however, concludes that the sugar radical in amygdalin is probably not allied to maltose but rather to a disaccharose, *gentiobiose*, and that emulsin preparations commonly contain a separate enzyme *gentiobiase*. It is also probable that the hydrolysis of the fructosides and galactosides is brought about by specific enzymes, occurring together with the enzymes which act upon the glucose derivatives.

Until recently emulsin was the only enzyme known which produced hydrocyanic acid as a result of its action, but recently other 'cyanogenetic' enzymes have been discovered, notably *lotase* by Dunstan and Henry,¹ and *gynocardinase* by Power and Lees.

The other enzymes of the class under consideration are not of such general interest as emulsin, although the glucosides upon which they act are of the most diverse kinds, as will be seen from the table. The enzyme which acts upon the glucoside 'indican' is of considerable industrial importance. It was formerly believed that indigo-white was formed in the reaction, but Hazewinkel² states that the product is indoxyl. Other enzymes which apparently belong to this class have been described by Schweitzer. They bring about the hydrolysis of substances known as *kolanin* and *cacaomin*, the products being either caffeine or theobromine together with glucose and a substance known as kola-red.

*Enzymes causing the hydrolysis of Proteins, their derivatives,
and the Purine bases.³*

Enzyme.	Substrate.	Products.	Principal Occurrence.
Trypsin	Proteins, proteoses and peptones, polypeptides	Amino-acids and simpler polypeptides	Pancreatic secretion
[Enterokinase Pepsin	Trypsinogen Proteins and some albuminoids	Trypsin { Proteoses Peptones Amino-acids	Intestinal juice] Gastric secretion
Papain	Proteins	Amino-acids	Juice of Carica Papaya
Bromelain	Proteins	Amino-acids	Pine apple fruit
Erepsin	Proteoses, peptones	Amino-acids	Intestinal mucosa
Arginase	Arginine	Ornithine and urea	Liver and kidney
Guanase	Guanine	Xanthine	Spleen, thymus, and liver
Adenase	Adenine	Hypoxanthine	Spleen, thymus, and liver

Trypsin and pepsin are the two most important enzymes connected with protein hydrolysis. Their action is in many respects similar, and their points of difference are quantitative rather than qualitative.

Pepsin is the enzyme chiefly concerned in gastric digestion. It is secreted by glands in the mucous membrane of the stomach, and

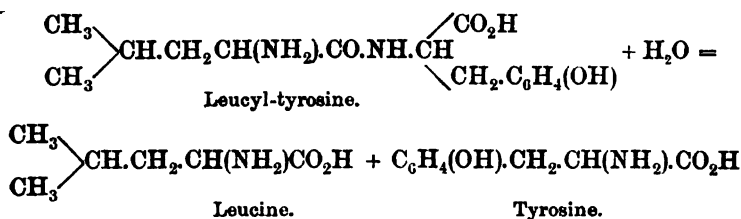
¹ Dunstan and Henry, *Proc. Roy. Soc.*, 1901, 67, 224; 68, 374.

² *Chem. Ztg.*, 1900, 24, 409.

³ To understand the nature of the proteins and purine bases, the student should read the two chapters which follow.

acts best in the presence of hydrochloric acid (0.2 per cent.), which is also secreted by special cells in the mucous membrane. Pepsin, under ordinary conditions, causes a rapid hydrolysis of the complex proteins with the formation of proteoses and peptones. If, however, the digestion is very prolonged the latter are to some extent decomposed and the simple amino-acids, such as leucine, tyrosine, &c., are formed.

Trypsin, on the other hand, acts best in an alkaline medium, and, although proteoses and peptones are formed as intermediate products, they rapidly undergo further hydrolysis producing amino-acids, together with certain *polypeptides* containing three or four amino-acid radicals linked together (see p. 410). Trypsin is also able to cause the hydrolysis of many of the synthetical polypeptides referred to on p. 412, particularly those obtained from the amino-acids of higher molecular weight. Thus, leucyl-tyrosine yields tyrosine and leucine, and the reaction is probably typical of most of the changes involved in the hydrolysis of a complicated protein.



More definite evidence is available as to the successive stages in the elaboration of trypsin than is the case with any other enzyme. The production of granules, which are believed ultimately to furnish trypsin, may be observed in the cells of the pancreas. The pure secretion of the pancreas is, however, practically devoid of action upon proteins; but if it be mixed with a trace of intestinal juice a digestive fluid of extraordinary power is obtained. The researches of Pawlow and of Bayliss and Starling¹ have conclusively shown that the intestinal mucosa furnishes an enzyme *enterokinase* which has the property of converting the inactive trypsinogen, the precursor or 'zymogen' of trypsin, present in the pancreatic juice, into the active trypsin. Enterokinase is therefore a 'ferment of ferments', and at present no other similar enzyme is known.

The secretion of pancreatic juice, and therefore of trypsin, is not

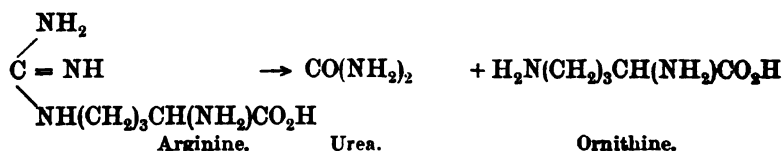
¹ Bayliss and Starling, *Journ. Physiol.*, 1904, 30, 61; 1905, 32, 129.

continuous, but is regulated by a simple chemical mechanism according to the needs of the organism. Bayliss and Starling¹ have been able to prove that the acid in the food passing from the stomach liberates a definite chemical substance, *secretin*, from the cells of the duodenal mucous membrane, and this, upon absorption, evokes a profuse secretion of the pancreas, containing all the enzymes normally present.

Besides trypsin and pepsin many other enzymes are known which cause the hydrolysis of proteins. Most animal tissues contain intracellular proteases, which are also found in many plants and fruits (papain, bromelin) and in some bacteria. The 'carnivorous plants' are also able to hydrolyse their protein food by means of enzymes.

A peculiar enzyme has been described by Cohnheim,² which is said to have the property of causing the hydrolysis of proteoses and of peptones, but is without action upon the ordinary proteins. It occurs in the small intestine, and its action is supposed to supplement that of trypsin, but it has not been very carefully studied.

Arginine is constantly present in the products of hydrolysis of proteins. An enzyme *arginase*, which occurs principally in the liver, is able to decompose arginine into ornithine and urea:



Arginase is also able to convert guanidine into urea and ammonia. It is the only urea-forming enzyme which has so far been isolated, but it is very probable that others exist.³

Many tissues also contain enzymes which are able to remove ammonia from the amino-acids resulting from protein hydrolysis. This reaction is of great biological importance, but it has not yet been possible to follow the changes completely.

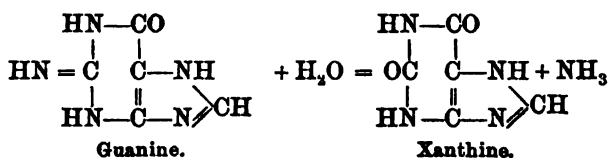
The question of the existence of enzymes which act upon the purine bases (see p. 867) has recently attracted much attention, and at least one definite enzyme, *guanase*, has been isolated by Jones,⁴ which is able to convert guanine into xanthine with loss of ammonia.

¹ Journ. Physiol., 1902, 28, 325.

² Zeit. physiol. Chem., 1902, 35, 184.

³ Koesel and Dakin, Zeit. physiol. Chem., 1904, 41, 321.

⁴ Zeit. physiol. Chem., 1904, 42, 35 and 343.

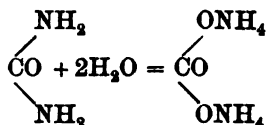


In a similar fashion adenine is converted into hypoxanthine, although it is not quite certain whether this change is due to the same enzyme that acts upon guanine or to a specific *adenase*.¹

There is also some evidence of the existence of enzymes occurring among the products of hydrolysis of nucleic acids which act upon the pyrimidine bases, such as cytosine.

The purine and pyrimidine bases are also attacked by oxidising enzymes accompanying guanase and adenase, and will be referred to under the head of 'oxidases'.

Two important enzymes, which have not yet been considered, are urease and lipase. Urease converts urea into ammonium carbonate.



The enzyme is found in media in which the *micrococcus ureae* or certain other organisms have grown, and is responsible for the ammoniacal fermentation of stale urine. The enzyme readily diffuses from the cells of the dead organisms, and may be roughly isolated by precipitation of the filtered liquid with alcohol. The conversion of ammonium carbonate into urea—the opposite change to that brought about by urease—is known to take place in the animal body. The change may be shown to occur when a 'surviving liver' is perfused with blood containing ammonium carbonate or carbamate, but, up to the present, it has not been possible to isolate the enzyme or to demonstrate the reaction except in the presence of intact liver cells.

Lipase is a widely distributed enzyme, and has the property of causing the hydrolysis of fats and certain derivatives of fats such as lecithin. It is found in the pancreatic juice, liver, and blood of animals, and in most oily seeds, particularly during germination. There appear to be distinct differences between the enzymes from different sources. Lipase is not only able to hydrolyse fats, but also many esters, such as ethyl acetate, ethyl carbonate, ethyl

¹ Cp. Schittenhelm, *Zeit. physiol. Chem.*, 1905, 45, 121 and 152.

salicylate, salol, &c. If a *d*-ester of an asymmetrical acid be hydrolysed by lipase, the two forms are attacked at unequal rates¹ (see p. 79); a similar selective hydrolysis has been observed by Fischer in the hydrolysis of racemic polypeptides by trypsin. The action of lipase has been shown to be reversible (see p. 866).

It has been stated that lipase may be separated into two substances—a heat-stable dialysable substance and an unstable non-dialysable substance. Neither body alone is able to bring about the hydrolysis of esters, but the reaction takes place in the presence of both substances. Many other facts are known which support the idea that enzyme activity in general is due to two or more substances acting conjointly, and in some cases the second substance or *co-ferment* appears to be inorganic (see p. 860).

The Oxidising Enzymes (Oxidases).

<i>Enzyme.</i>	<i>Substrate.</i>	<i>Products.</i>	<i>Principal Source.</i>
Alcohol oxidase	Alcohol	{ Acetic acid (Acetaldehyde)	Bact. Xylinum Bact. Aceti, &c.
Aldehydase	Aldehydes	Acids	Liver
Tyrosinase	Tyrosine	{ Homogentisic acid, Black colouring matter	Plants, e.g. Dahlia, certain fungi
Laccase	Urushic acid	Varnish	Juice of lac-tree
Xanthine-oxidase	{ Xanthine Hypoxanthine	Uric acid	Liver and spleen
Uricolase	Uric acid	Allantoin ²	Liver

The oxidases are an ill-defined class of enzymes, which enable free oxygen to effect oxidations which would not otherwise take place. Although oxidation must obviously play an extremely important part in the metabolism of living cells, our knowledge of the mechanism of the process is extremely meagre. This is partly due to the fact that it is only in comparatively few cases that the action of an oxidising enzyme has been followed under fairly normal conditions. It is well known that many animal tissues are able to convert, to some extent, aldehydes into acids, a change which has been studied with benzaldehyde, salicylaldehyde, and formaldehyde; the presence of oxidases is also inferred from the fact that the same tissues are able to form indophenol colouring

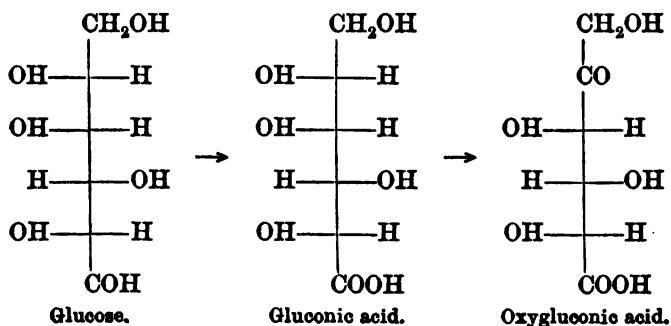
¹ Dakin, *Journ. of Physiol.*, 1908, 30, 253; 1905, 32, 199; *Proc. Chem. Soc.*, 1908, 19, 161.

² *Beitr. chem. phys. u. path.*, 1907, 9, 295.

matters when they are digested with an alkaline mixture of α -naphthol and alkyl *p*-phenylenediamines. It is, however, questionable as to how far results obtained by reactions of this nature are comparable with those effected by the enzymes working under normal conditions and acting upon their usual substrates.

Acetic fermentation is one of the simplest biochemical oxidations, and is readily brought about by *bacillus aceti* and other bacteria. The conversion of alcohol into acetic acid by the organism appears to take place in stages, as acetaldehyde is frequently formed. The *bacillus aceti* is not only able to oxidise alcohol, but can convert glucose into gluconic acid, glycol into glycollic acid, and mannitol into fructose. Another organism, *B. xylinum*, which commonly causes acetic fermentation is said to be identical with the 'sorbose bacterium' of Bertrand, referred to on p. 299.

The sorbose bacterium, in addition to its action on polyhydric alcohols, is able to oxidise many aldehydes to the corresponding acids, and if, as in the case of gluconic acid, a secondary alcohol group, capable of attack, is present, the final product of the reaction will be a ketonic acid.

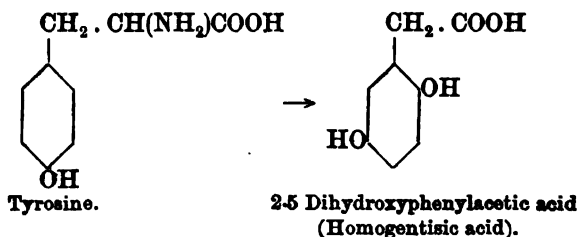


Oxidation in the absence of the living cells has been recently observed by Buchner and Meisenheimer,¹ who were able to prepare an active preparation from the cells of the dead bacteria, and there can be little doubt that the active agents in these changes are enzymes, comparable in every way with those that cause alcoholic fermentation.

Tyrosinase and laccase are vegetable oxidases which are closely allied and often occur together. The former converts tyrosine (α -amino- β -hydroxyphenyl-propionic acid), a common constituent of proteins, into a black, insoluble substance, of unknown constitution,

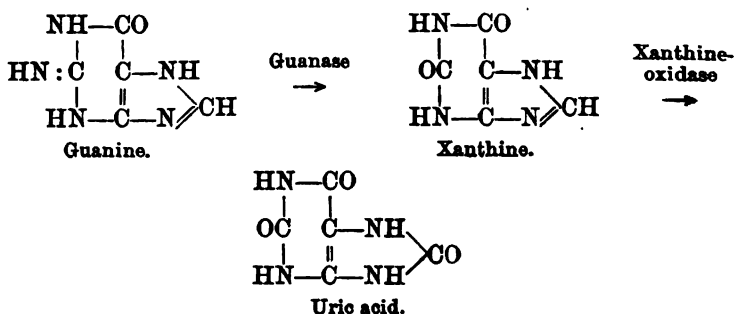
¹ Ber., 1908, 36, 684.

the formation of which appears to be preceded by that of 2-5 dihydroxyphenylacetic acid (homogentisic acid).



This reaction indicates a curious shifting of the position of the para hydroxyl group. It is of interest to note that in certain pathological conditions the tyrosine present in protein food is converted into homogentisic acid, which is found in the urine. Laccase converts urushic acid, contained in the light coloured juice of the lac-tree, into a deep black varnish-like substance of unknown composition. Both tyrosinase and laccase are also able to oxidise polyhydric phenols, such as pyrogallol and quinol, but laccase is without action upon tyrosine.

Two distinct oxidases are known which are concerned in the oxidation of substances belonging to the purine group. The first is named *xanthine-oxidase*, and is able to bring about the oxidation of xanthine or hypoxanthine to uric acid, whilst the second enzyme carries the oxidation of uric acid further, forming products among which allantoin has been identified. Xanthine-oxidase occurs alone in the spleen, but both enzymes are found together in the liver. The existence of enzymes (guanase, adenase) which can convert guanine and adenine into hypoxanthine and xanthine has already been mentioned (p. 352), and it is therefore clear that by the combined action of these ferments it is possible to convert any of the four xanthine bases, commonly occurring in the animal body, into uric acid, a fact which is doubtless of great physiological significance.



The large part that glucose plays in cell metabolism long ago suggested that enzymes must exist which have the power of oxidising, or at least decomposing, the simpler sugars. A number of these bodies have been described under the name of *glycolytic enzymes*. Unfortunately, the experimental difficulties connected with this kind of investigation (arising from bacterial contamination) are so great that grave doubts are entertained as to the correctness of many of the results. Certain investigators, such as Stoklassa and Czerny,¹ assert that these enzymes are widely distributed; Cohnheim² and others are of opinion that their action may be observed in preparations obtained from a certain combination of tissue extracts, whilst Claus and Embden³ have completely failed to confirm any of these results. Until, therefore, further experimental evidence is available, it is impossible to come to a definite conclusion, but it is at least certain that excellent *a priori* grounds exist for believing that important enzymes of this type actually occur.

It has usually been assumed that the colourless products resulting from the hydrolysis of indican were converted into indigo-blue, through the action of a specific oxidase contained in the leaves of the indigo plant; but the separate existence of this enzyme has recently been questioned.

That most vegetable and animal tissues possess the power of causing the decomposition of hydrogen peroxide has been known for a long time. It seems likely that this reaction is due to a special enzyme *catalase*, which has been roughly isolated in two different forms by Loew. Certain other oxidases, however, are also able to produce the same decomposition. Catalase has usually been classed amongst the oxidases, but it is questionable if the enzyme plays any part in oxidative processes; more probably, its function is to remove the traces of hydrogen peroxide, which are constantly formed as a by-product in other oxidations.

Many other vegetable oxidases have been described, including the so-called 'peroxidases' which activate hydrogen peroxide and possibly other peroxides, and so induce reactions which the peroxide alone could not accomplish. Numerous systems for classifying these enzymes have been proposed, but they have at present a limited chemical interest, for it is not clear what type of reaction they normally induce nor upon what kind of substances they act.⁴

¹ *Centralbl. f. Physiol.*, 18, 798.

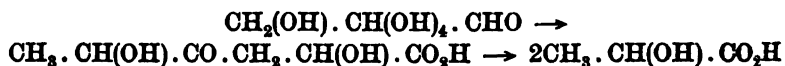
² *Zeit. physiol. Chem.*, 1904, 42, 401.

³ *Beitr. z. physiol. u. path. Chem.*, 1905, 6, 214.

⁴ A review of work upon the vegetable oxidases will be found in a 'Sammelreferat' by Bach and Chodat, *Biochem. Centralbl.* i, 1908, Nos. 11 and 12.

Reductases. The property which some animal tissues possess of effecting certain reductions, such as the conversion of the colouring matter, methylene blue, into a colourless leuco-base, has long been known; but it has not been possible to satisfactorily isolate the reducing agent. Rey-Pailhade has shown that certain organisms, such as yeast, are able to convert free sulphur into hydrogen sulphide, and this is believed by some to be caused by a reducing enzyme. The conversion of nitrates into nitrites and of nitrobenzene into aniline has also been carried out with extracts of animal tissues, but the satisfactory isolation of a reducing enzyme has not yet been accomplished.

Alcoholic Fermentation. Alcoholic fermentation has been studied more extensively than perhaps any other biochemical change, and a brief outline of some few of the earlier investigations has already been given. The various chemical reactions involved in the conversion of glucose into alcohol and carbon dioxide are not easy to picture, and various hypotheses have been suggested at different times. It will be seen, on comparing the structure of the sugar and of the resulting products, that intramolecular rearrangements of a peculiar kind must occur, for although the final result of the reaction cannot be considered either as an oxidation or as a reduction, yet both oxidation and reduction of some of the groups attached to different carbon atoms must take place. As long ago as 1870 Baeyer¹ suggested a scheme in which some of the oxygen molecules of the sugar were supposed to 'wander', and this intramolecular change was ascribed to the production of a hypothetical substance which was rendered unstable by the local accumulation of the oxygen atoms, and which could therefore be readily resolved into simpler products. Quite recently Buchner and Meisenheimer² concluded, from the fact that a little lactic acid is constantly formed during alcoholic fermentation, that this substance is an intermediate product in the reaction. Slightly modifying Baeyer's hypothesis, they represented the formation of lactic acid as derived from a hypothetical dihydroxy γ -ketonic acid:

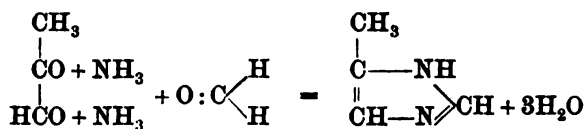


At about the same time experimental evidence of the mechanism of the conversion of glucose into lactic acid, by purely chemical means,

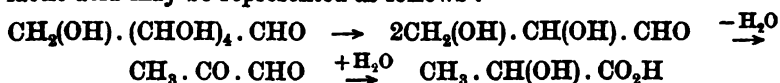
¹ *Ber.*, 1870, 3, 68.

² *Ber.*, 1904, 37, 417.

was obtained by Nef,¹ who was able to show that pyruvic aldehyde was an intermediate product of the action of caustic soda upon glucose—a reaction which had long been known to yield lactic acid. It is of interest to note in this connection that traces of alcohol are formed, under certain conditions, when caustic soda acts upon invert sugar. Knoop and Windaus² have also shown that pyruvic aldehyde is apparently readily formed from glucose. They proved that, when zinc ammonium hydroxide acts upon glucose in sunlight at the ordinary temperature, a large quantity of methyliminazole is produced, and the production of this substance is readily explained on the assumption of the intermediate formation of pyruvic aldehyde and of formaldehyde.



It therefore appeared not improbable that pyruvic aldehyde might be an intermediate product in the breaking down of the sugar molecule in alcoholic fermentation, and Buchner and Meisenheimer³ have recently supported this view. According to Wohl the formation of lactic acid may be represented as follows :



Glyceric aldehyde, which is supposed to be first formed, parts with water and gives pyruvic aldehyde. The latter then reunites with the elements of water forming lactic acid. The conversion of lactic acid into alcohol and carbon dioxide is an easily understood change, and, according to Buchner, separate enzymes may be concerned in its formation and decomposition. The formation of glyceric aldehyde as an intermediate product and its fermentability by yeast is not compatible with Wohl's view ;⁴ but if the supposition is correct, it is difficult to explain why lactic acid itself is practically non-fermentable. This, however, need not imply that in the intramolecular rearrangements of the sugar molecule a 'potential' formation

¹ *Annalen*, 1904, 335, 254, 279.

² *Beitr. z. Chem. Phys. u. Path.*, 1905, 6, 392.

³ *Ber.*, 1905, 38, 620.

⁴ *Ber.*, 1898, 31, 1800. Emmerling has denied the statement that yeast is able to ferment glycerose, and states that perfectly fresh 'glycerose' does not ferment unless warmed or treated in some way which might cause condensation and so give rise to a fermentable hexose. Bertrand has, however, shown recently that pure glycerose does ferment, but with difficulty.

of lactic acid does not occur; in other words, the arrangement of the atoms at a particular stage may be such, that if the reaction then ceased lactic acid would be formed.

A fact of extreme interest, as showing the relation existing between enzymes and the molecular configuration of the substances upon which they act, is the observation that only sugars with 3, 6, or 9 carbon atoms can undergo fermentation, and also that among the hexoses, only the four naturally occurring sugars, *d*-galactose, *d*-mannose, *d*-glucose, and *d*-fructose, which have closely related configurations, are directly fermentable (p. 326).

As previously mentioned, the first convincing evidence of the dependence of alcoholic fermentation on an enzyme, comparable in every way with 'unorganised ferments', was furnished by Buchner. Buchner's method consists in rupturing the cells by grinding the yeast with sand and kieselguhr (diatomaceous earth), and then expressing the juice under very high pressure. The cell-free juice or 'press juice' so obtained is able to ferment a limited amount of sugar. The small quantities of succinic acid, which are produced in ordinary yeast fermentation, are apparently not formed in the absence of living cells, although traces of glycerine occur.

A. Harden and W. T. Young¹ observed that the addition of old or boiled cell juice, which contained no enzymes, greatly increased the fermenting activity of fresh cell juice. Further investigation showed that the activating substance was a complex organic phosphate. E. Buchner, as well as Harden and Young, found that a similar effect could be obtained by the addition of inorganic phosphates. An activating substance of this kind is often referred to as a *co-ferment*.

Buchner and Albert found that yeast cells may be killed by treatment with alcohol and ether or with acetone, without destroying the intracellular enzymes. Preparations of this kind are much more active than those derived from the juice obtained by pressure.

Acid Fermentations. In addition to acetic fermentation, which has already been mentioned, several fermentations are known in which substances belonging to the carbohydrate group are converted into hydroxy-acids or acids of the acetic series. The production of acids, especially lactic acid, in many fermentative processes was early recognized, but it was reserved for Pasteur to show the connection

¹ *Proc. Physiol. Soc.*, Nov. 1904, 1-2; *Journ. Physiol.* 1904, 32, 1; *Proc. Chem. Soc.*, 1905, 21, 189.

existing between specific organisms and the production of lactic acid, and also to prove that the process was quite distinct from alcoholic fermentation. The power to produce lactic acid from sugars is not confined to the *B. acidilactici* of Pasteur, but is shared by quite a large number of organisms of various kinds, though the relative yields of lactic acid vary enormously with different bacteria. The reaction is brought about by an enzyme, which has been shown to be active, even after the cells of the organism have been killed by acetone.¹

Lactic acid may be formed from glucose, fructose, galactose, and at least one pentose, rhamnose; also from mannitol, dulcitol, and sorbitol, as well as from inositol (hexahydroxy-hexahydrobenzene). The manner in which lactic acid is produced from sugar, already discussed in connection with alcoholic fermentation, is not easy to understand (cp. p. 858). If the view there put forward is correct, the lactic acid should be inactive, as the asymmetry originally present in the sugar molecule is lost. Until recently this was commonly assumed to be the case, but McKenzie² has found that most fermentation lactic acid is distinctly dextro-rotatory. This result might, however, be explained on the basis of an initial formation of inactive lactic acid, followed by a selective conversion of a portion of the laevo-acid into other products. Frankland and MacGregor³ have, in fact, shown that such a resolution of inactive lactic acid may be brought about by some organisms.

Butyric fermentation is associated with separate organisms from those that cause lactic fermentation, but the two classes of bacteria are frequently found together. Butyric acid is formed from lactic acid and also from a large number of those substances which readily yield lactic acid under the influence of bacteria. The mechanism of butyric fermentation, which is usually accompanied by the evolution of hydrogen, is much more complicated than that of acetic or lactic fermentation.

Under the influence of certain other organisms lactic acid may be made to yield other saturated acids, such as acetic, propionic, and valeric acids. Special organisms are also known which form citric and oxalic acids, when grown in glucose solutions, but the chemistry of these reactions is still obscure.⁴

¹ Buchner and Meisenheimer, *Ber.*, 1908, 36, 684; Herzog, *Zeit. physiol. Chem.*, 1908, 87, 881.

² *Trans. Chem. Soc.*, 1905, 87, 1878.

³ *Trans. Chem. Soc.*, 1898, 68, 1028.

⁴ A very large amount of work has been devoted to following the biochemical changes which the lower organisms are able to effect. Reactions like those

Clotting Ferments. Reference must be made to a curious class of enzymes which bring about the clotting of certain substances. The best known of these are *thrombase*, the blood clotting ferment, *rennin*, which causes the clotting of milk, and *pectase*, which acts upon certain complicated carbohydrates occurring in plants. In the case of all of these enzymes it is found that calcium salts play an important part in the reaction. In the case of thrombase the calcium salts appear to convert the zymogen, or precursor of the enzyme, into the active enzyme, just as enterokinase converts trypsinogen into trypsin, with the difference that enterokinase has itself the properties of an unstable enzyme. The calcium salts may be said to act as a 'co-ferment'. The clotting of blood is a phenomenon which has been closely studied by physiologists, and consists in the conversion of a colourless, globulin-like substance, *fibrinogen*, into a white stringy protein *fibrin*. It has been possible to roughly isolate the zymogen of the enzyme, and to observe its conversion into active thrombase on addition of calcium salts.

The action of rennin appears to be somewhat different. Rennin is chiefly derived from the gastric mucosa of mammals, and has been used for a very long time for curdling milk in the manufacture of cheese. The enzyme is formed from a zymogen by the action of the acids of the stomach, and not by the action of calcium salts, as in the case of thrombase. The clotting of milk or of a caseinogen solution involves two distinct reactions—firstly, the conversion by the enzyme of the caseinogen into a soluble protein closely allied to casein, and secondly, the conversion of this substance into an insoluble clot by the action of calcium salts.

If a solution of caseinogen, free from calcium salts, is digested with pure rennin no clotting occurs, but if traces of calcium salts are added, the liquid may be caused to clot even after the enzyme has been destroyed by boiling.¹ It is not certain whether the reactions brought about by the clotting enzymes involve simply a change in physical condition, or whether some chemical reaction takes place as well.

brought about by the nitrifying bacteria are of the utmost economic importance, whilst the substances produced by the different putrefactive and pathogenic bacteria have an important bearing upon the causation of disease. Reference should be made to works on Bacteriology for particulars of these and similar topics, which would be beyond the scope of this essay.

¹ To avoid confusion it is important to remember that many continental writers employ Hammarstein's nomenclature, and term the original substance acted upon by the enzyme 'casein' and the product of the action of the enzyme 'paracasein'.

Anti-Enzymes. Mention must be made of this interesting class of substances, the existence of which has only recently been definitely established. The anti-enzymes are of importance since they form a connecting link between the toxins and enzymes. It is well known that if an animal is injected with small but gradually increasing quantities of the poisonous toxins, extracted from the cells of an organism, such as that which causes tetanus, the animal rapidly acquires a degree of immunity, which in some cases is very great. It is found that this immunity is due to the production of definite substances, which may be found in the blood, and which have the power of combining with the toxin, and so preventing its further action. These bodies are known as anti-toxins, and are of the greatest importance in pathology. In a similar way it is found that injection of certain enzymes into an animal is followed by the appearance in the blood of substances which are able to inhibit the reaction normally brought about by the enzyme. For example, it is found that blood-serum containing anti-pepsin has a powerful action in hindering or almost entirely preventing the action of pepsin upon proteins. Some of these *anti-bodies* are of great importance; for their presence in the blood explains the resistance of protein containing tissues of the body to the protein digesting enzymes of the alimentary tract.

So far it has been possible to obtain anti-bodies for the following enzymes: trypsin, pepsin, lipase, emulsin, urease, lactase, tyrosinase, thrombase, and rennin. These anti-bodies are essentially specific—that is, they only inhibit the action of the particular enzyme used in their preparation. The ‘lock and key’ simile of Fischer might be applied to the enzymes and anti-bodies as well as to the enzymes and their substrates. It has been possible to distinguish enzymes such as animal and vegetable rennin¹ which are otherwise indistinguishable, owing to the fact that their respective anti-bodies were not interchangeable, and this biological method of investigation will no doubt be of service in the future.

Mechanism of Enzyme Action.² It has already been pointed out that, according to the law of mass action applied to monomolecular, non-reversible changes, the following equation holds (p. 208):

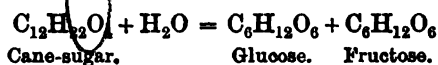
$$k = \frac{1}{t} \log \frac{a}{a-x}.$$

¹ Morgenroth, *Centraltb. d. Bakter.*, 26, 349; 27, 721.

² For the kinetics of enzyme action see *Chemical Statics and Dynamics*, p. 353, by J. W. Mellor. (Longmans.)

Wilhelmy,¹ in his classical investigation which appeared in 1850, showed that the inversion of cane-sugar by acids follows the mass law.

The process is represented by the following equation, which is apparently dimolecular:



But if the solution is dilute the amount of water is practically constant, and the reaction may therefore be treated as monomolecular and it is also non-reversible.

By observing the change of rotation on the addition of a minute quantity of hydrochloric acid the following numbers were obtained:

t in minutes.	Deviation.	Concentration per cent.	$\log a - \log (a-x)$.	k .
0	+46.75°	65.45		
15	48.75	62.45	.0204	.00136
30	41.00	59.70	.0899	.00183
45	38.25	56.95	.0605	.00184
60	35.75	54.45	.0799	.00183
75	33.25	51.95	.1003	.00184
90	30.75	49.45	.1217	.00135
105	28.25	46.95	.1441	.00137
120	26.00	44.70	.1655	.00137
∞	-18.70			

The velocity (k) is constant, or, in other words, with a decreasing quantity of cane-sugar there is a proportionate decrease in the quantity inverted in unit of time, and the curve represented by the values of t and x is logarithmic.

Other acids give similar results, although the rate of inversion varies with different acids. As the rate of inversion appears to be directly proportional to the electrical conductivity of the acids in question, the process has been ascribed to the action of hydrogen ions, though it does not seem probable that the velocity of enzyme action is conditioned by the presence of ions.

The hydrolysis of cane-sugar by invertase was first submitted to quantitative examination by O'Sullivan and Thompson² in 1890. Using the optical method of Wilhelmy, they found that the velocity (k) increases slightly until 80 per cent. of the sugar had been hydrolysed and then decreases. Nevertheless, they drew the general conclusion that, in spite of these small deviations, the reaction follows the mass law. The subject was reinvestigated in 1902 by

¹ Pogg. Ann., 1850, 81, 413, 499; Ostwald's *Klassiker*, No. 29.

² Trans. Chem. Soc., 1890, 57, 884.

A. J. Brown,¹ who found that the velocity is not a constant, but that a given quantity of invertase decomposes a nearly constant weight of sugar in unit of time. Thus, in one hour, using different strengths of sugar solution, the following quantities were inverted :

Grams per 100 c.	Grams inverted.
4.89	1.280
9.85	1.855
19.91	1.855
29.96	1.285
40.02	1.076

This is contrary to the mass law, according to which the greater the concentration the greater should be the quantity inverted. It was further observed that, after a certain proportion of sugar had been inverted, the linear period (or equal weights in equal times) is succeeded by a logarithmic period (or a decreasing quantity in equal times) in which the velocity (k) is approximately constant. This change of velocity accompanying the inversion of cane-sugar in the earlier and later stages of the process was also observed by A. J. Brown² during the fermentation of sugar by yeast ; by H. T. Brown and Glendinning³ in the action of diastase on starch, and by E. F. Armstrong⁴ during the hydrolysis of milk-sugar by the enzymes, lactase and emulsin, and of maltose by maltase. In each case there was a linear followed by a logarithmic period. What is the reason of the slowing down of the process ? It cannot be that the mass law is untrue, and the cause must be looked for elsewhere. A. J. Brown suggested that the substance undergoing change unites with the enzyme previous to composition, after which the enzyme is liberated, and can unite with more substance, and so forth. That such a union is highly probable has been shown by O'Sullivan and Tompson, who found that invertase survives a much higher temperature when cane-sugar is present than when absent, and by the observations of Fischer and others on the selective action of enzymes. If the amount of enzyme is large and the process of combination instantaneous, or very rapid in comparison with the subsequent rate of hydrolysis, the velocity (k) would still be constant. The only change in the effect would be that the substance and enzyme would be changing together instead of the substance alone. If, however, the amount of enzyme is small compared with that of the substance, only a portion of the substance, namely that in union with the enzyme, would change, and, until the substance had diminished below a certain amount, equal quantities would undergo hydrolysis in equal times. Both A. J.

¹ *Trans. Chem. Soc.*, 1902, 81, 373.

² *Trans. Chem. Soc.*, 1902, 81, 888.

³ *Trans. Chem. Soc.*, 1892, 61, 369.

⁴ *Proc. Roy. Soc.*, 1904, 73, 500.

Brown and E. F. Armstrong have shown that the curve becomes logarithmic or linear according to the proportion of enzyme present. Another possible cause affecting the mass law, also suggested by A. J. Brown, might be due to the accumulation of the products of hydrolysis which by union with the enzyme would withdraw it from its sphere of action. The correctness of this view has received strong corroboration from the recent researches of E. F. Armstrong,¹ who has shown that the action of the enzyme is only retarded by the presence of those hexoses which are derived from the hydrolysis of the disaccharose or glucoside undergoing change.

Galactose, for instance, retards the hydrolysis of β -galactosides (e.g. milk-sugar) by lactase, whilst glucose and fructose are inert. Glucose retards the hydrolysis of α -glucosides (e.g. maltose), while fructose has no action. The previous experiments of Henri² have also clearly shown that the retarding action of invertase on cane-sugar is determined by the nature of the product, for of the two, glucose and fructose, the latter alone retards the process. Finally, the process of reversion must be considered as a cause of retardation in enzyme action. The suggestion was first made by Croft Hill³ when studying the hydrolysis of maltose by maltase. He found that not only the addition of glucose retards the process, but that maltase has the power of converting glucose into the isomeric disaccharoses, namely revertose and probably maltose (p. 846).

The reversibility of enzyme action has been proved in other cases. Emmerling⁴ has shown that amygdalin is formed when yeast maltase is added to a solution of glucose and mandelic nitrile glucoside (p. 849), and Kastle and Loevenhart⁵ have obtained ethyl butyrate by the action of lipase on ethyl alcohol and butyric acid, that is, by the enzyme which produces the two latter products by hydrolysis.

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¹ *Proc. Roy. Soc.*, 1904, 73, 516.

² *Trans. Chem. Soc.*, 1898, 73, 684.

³ *Amer. Chem. J.*, 1900, 24, 491.

⁴ *Compt. rend.*, 1901, 123, 891.

⁵ *Ber.*, 1901, 34, 8810.

CHAPTER X

THE PURINE GROUP

Historical. The history of the group of compounds which forms the subject of the present chapter has its origin in those curious pathological concretions which are found in the human body, as chalk-stones and urinary calculi. The composition of these substances attracted the attention of the early physicians and chemists, who speculated freely on their origin without discovering much about their chemical nature. It is curious to find that Paracelsus regarded them as having a similar origin to the lees of wine, and named them *tartar*.¹ The discovery in urinary calculi of uric acid, or as it was then termed *lithic acid*, is due to Scheele, who isolated the acid in 1766 and observed at the same time the red colour which it gives on evaporation with nitric acid. Prout² afterwards noticed that ammonia changes the colour to violet, forming *murexide*, a reaction which is still used as a delicate test for the acid. In 1798 Pearson found uric acid in the deposit which sometimes forms in the tissues of persons suffering from gout, and since then its occurrence has been observed in many different parts of the body. It is found in variable amount in the urine of most animals, and constitutes the bulk of the excreta of birds and reptiles. It is an interesting fact that the white colour on the wings of butterflies, known as *White Pieridae*, is due to uric acid.

Decomposition Products of Uric Acid. In 1798 Fourcroy observed the formation of urea when chlorine water acts upon uric acid; a little later Brugnatelli obtained a crystalline compound, now known as *allozan*, by the action of nitric acid; its elementary composition,³ $C_5H_4N_4O_8$, was determined in 1834 by Liebig and Mitscherlich. But the first serious contribution to our knowledge of uric acid is contained in a remarkable memoir by Wöhler and Liebig,⁴ entitled 'Untersuchungen über die Natur der Harnsäure', which was published

¹ *Treatise on Chemistry*, by Roscoe and Schorlemmer, vol. iii, part ii, p. 331.

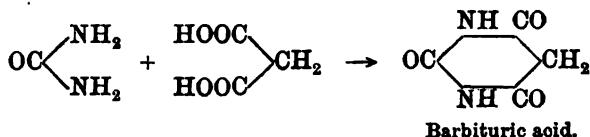
² *Phil. Trans.*, 1818, p. 420.

³ The modern formulae are used.

⁴ *Annalen*, 1838, 26, 241.

in 1838, and still serves as a model of scientific acumen and experimental skill. They showed how uric acid by regulated oxidation could be converted into a series of substances of diminishing complexity. Thus, by direct oxidation they obtained the three compounds, *allantoin* $C_4H_6N_4O_3$, *alloxan* $C_4H_2N_2O_4$, and *parabanic acid* $C_3H_2N_2O_3$. From alloxan they prepared by reduction *alloxantin*, $C_8H_8N_4O_8$, and *dialuric acid*, $C_4H_4N_2O_4$; by the action of ammonium sulphite, *thionuric acid*, $C_4H_6N_2SO_6$, and from the latter, by boiling with dilute mineral acids, *uramil*, $C_4H_6N_3O_3$. To this collection of what may be termed the fragments of the uric acid molecule, Schlieper¹ afterwards added several new compounds. As alloxan was found to undergo hydrolysis into mesoxalic acid and urea, Gerhardt suggested that its formula should be represented as mesoxalyl urea. But apart from this, little was known about the constitution of these various derivatives until the years 1863 and 1864, when Baeyer,² in a series of masterly researches, placed the whole subject in a clear light, and so prepared the way for the subsequent discovery of the structure and synthesis of uric acid and of the allied xanthine bases.

Without entering into detail, the manner in which Baeyer arrived at some of his results may be briefly indicated. Dialuric acid, obtained by reducing alloxan, is converted, on heating, into *hydrilic acid*, which may be regarded as an anhydride of alloxan and barbituric acid (see below). With nitrous acid, hydrilic acid is partly converted into *violuric acid*, and with nitric acid into *dilituric acid*. Both violuric acid and dilituric acid, on reduction, form uramil, and with bromine they yield the same product, which Baeyer first termed *alloxan bromide*, but afterwards altered to *dibromo-barbituric acid*. In the first case an isonitroso group, in the second a nitro group and a hydrogen atom are exchanged for two bromine atoms. Dibromo-barbituric acid on reduction forms *barbituric acid*. Now, since barbituric acid is decomposed with potash into urea and malonic acid, it is probably malonyl urea, a view which was afterwards confirmed by Grimaux,³ who synthesised it by heating together malonic acid, urea, and phosphorus oxychloride :

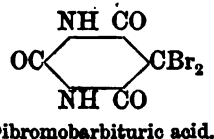
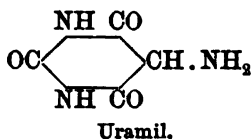
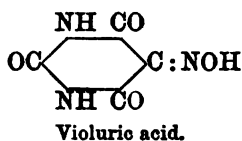
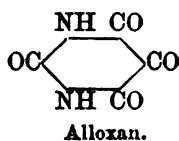
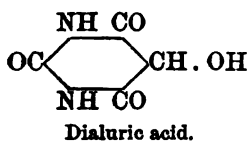


¹ *Annalen*, 1845, 56, 1.

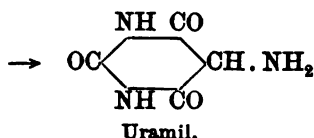
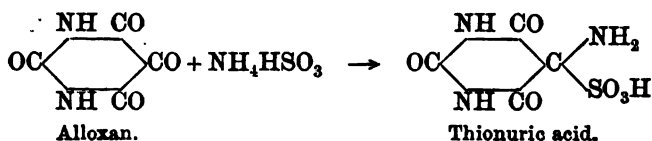
² *Annalen*, 1863, 127, 1, 199; 1864, 130, 129; 131, 291.

³ *Bull. Soc. Chim.*, 1876, 31, 146.

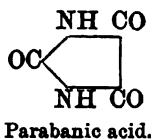
Baeyer represented the relation in which the compounds, referred to above, stand to barbituric acid by the following formulae:



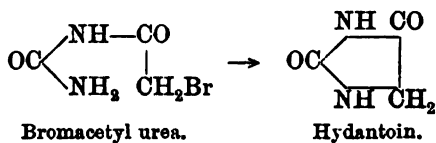
The constitution of thionuric acid is determined by its formation from alloxan and ammonium sulphite and its conversion into uramil.



The structure of parabanic acid is derived from its resolution into urea and oxalic acid, and its subsequent synthesis by Grimaux from these two substances with the aid of phosphorus oxychloride.



Hydantoin, or glycolyl-urea, which is formed by the reduction of allantoin, was synthesised by the action of ammonia on bromacetyl-urea by Baeyer, who thus prepared the first synthetical ureide.



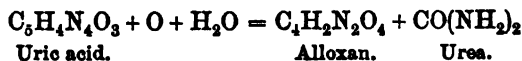
Baeyer divides the above compounds into two classes, the paraban series and the alloxan series.¹

<i>Paraban Series.</i>	<i>Alloxan Series.</i>	
Parabanic acid (Oxalyl-urea) Oxaluric acid	Alloxan (Mesoxalyl-urea) Dialuric acid (Tartronyl-urea) Barbituric acid (Malonyl-urea) Dibromo-barbituric acid	Violuric acid Dilituric acid Thionuric acid Uramil

In addition to the above, there is a series of diureides, which may be regarded as combinations of two molecules of certain of the above compounds. The exact nature of this union is not definitely known in every case.

Diureide.	Constituent molecules.	Probable formula.
Allantoin	Hydantoin + Urea	$ \begin{array}{c} \text{NH}_2 \quad \text{OC} \quad \text{NH} \\ \diagdown \quad \diagup \quad \diagdown \\ \text{OC} \quad \text{NH} \quad \text{CH} \quad \text{NH} \quad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{NH} \quad \text{CO} \end{array} $
Hydurillic acid	Alloxan + Barbituric acid	$ \begin{array}{c} \text{NH} \quad \text{CO} \quad \text{CO} \quad \text{CH}_2 \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{OC} \quad \text{NH} \quad \text{CO} \quad \text{CH} \quad \text{N} \quad \text{CO} \quad \text{NH} \quad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{NH} \quad \text{CO} \quad \text{CO} \quad \text{NH} \end{array} $
Alloxantin	Alloxan + Dialuric acid	$ \begin{array}{c} \text{NH} \quad \text{CO} \quad \text{HO} \cdot \text{C} \quad \text{NH} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{OC} \quad \text{NH} \quad \text{CO} \quad \text{C}(\text{OH}) \cdot \text{O} \cdot \text{C} \quad \text{CO} \quad \text{NH} \quad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{NH} \quad \text{CO} \quad \text{CO} \quad \text{NH} \end{array} $
Murexide ²	Alloxantin + Ammonia	$ \begin{array}{c} \text{NH} \quad \text{CO} \quad \text{CO} \quad \text{NH} \\ \diagdown \quad \diagup \quad \diagdown \quad \diagup \\ \text{OC} \quad \text{NH} \quad \text{CO} \quad \text{C} \quad \text{N} = \text{C} \quad \text{CO} \quad \text{NH} \quad \text{CO} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{NH} \quad \text{CO} \quad \text{CO} \quad \text{NH} \end{array} $
Violantin	Violuric acid + Dilituric acid	—

Structure of Uric Acid. As uric acid is found to break up on oxidation into equal molecules of alloxan and urea according to the equation :

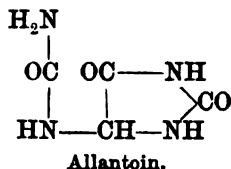


it would appear to be a compound of alloxan and urea, in which the two components are united with the loss of two hydroxyl groups.

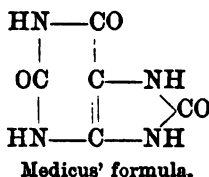
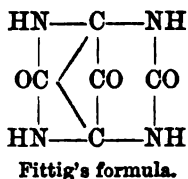
¹ For the special properties of the individual compounds a book of reference must be consulted.

² Möhlau, *Ber.*, 1904, 37, 2686; Piloty and Finckh, *Annalen*, 1904, 333, p. 22.

If the oxidation is carried out with neutral or alkaline permanganate, or with lead peroxide, the reaction takes a different course and allantoin is formed. Allantoin is a diureide, whose structure is known from its direct synthesis from glyoxalic acid and urea.¹



The presence of four imino groups in uric acid agrees with the existence of a tetramethyluric acid, obtained by the direct methylation of uric acid, from which all the nitrogen can be removed as methylamine on heating with strong hydrochloric acid. These facts have found expression in two formulae for uric acid, one proposed by Fittig² in his text-book, and the other by Medicus:³



Fittig's formula represents a symmetrical arrangement of two condensed pyrimidine nuclei, that of Medicus contains a fused pyrimidine and iminazole ring.

A clear indication of the correctness of Medicus' formula as opposed to that of Fittig was afforded by Fischer's⁴ discovery of a second monomethyluric acid, in addition to the one previously described by Hill,⁵ both of which are formed simultaneously by treating the lead salt of uric acid with methyl iodide. Since one of these compounds gives, on oxidation, methyl alloxan and urea, and the other, by similar treatment, alloxan and methyl urea, the formula of uric acid must be represented by the fusion of an alloxan and a urea nucleus, so as to form an unsymmetrical grouping as proposed by

¹ Grimaux, *Ann. Chim. Phys.*, 1877 (5), 11, 389.

It has been shown that allantoin is not a direct product of the oxidation of uric acid. It is probable that both of the ring systems in uric acid are broken on oxidation and that the allantoin is formed as the result of complicated intramolecular changes. This observation diminishes the value of the evidence afforded by the formation of allantoin.

² *Grundriss der organischen Chemie*.

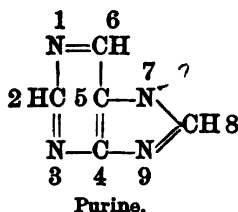
³ *Annalen*, 1875, 175, 236.

⁴ *Ber.*, 1884, 17, 1777.

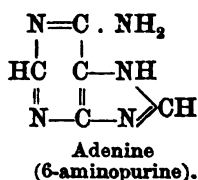
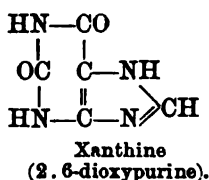
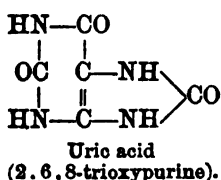
⁵ *Ber.*, 1876, 9, 370, 1090.

Medicus. According to Fittig's formula only one monomethyl uric acid should exist. The subsequent preparation of all the theoretically possible methyluric acids as well as the various syntheses of uric acid, to which reference will presently be made, have in every case confirmed the original formula assigned by Medicus, which is now universally accepted.

Nomenclature. Fischer has shown that the same atomic framework is present in uric acid and the numerous xanthine bases and denotes the relative position of the atoms by the numbers 1 to 9. If the four additional hydrogen atoms necessary to satisfy the valencies of the carbon and nitrogen atoms be added, the structure of the parent substance of the series is obtained, a compound which has been prepared by Fischer and named *purine* (*purum uricum*). This substance will be referred to later (p. 387).



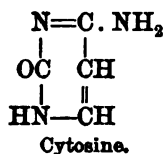
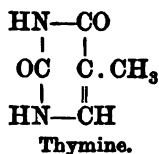
Uric acid and the xanthine bases may be regarded as substituted purines. As an illustration of the above system of nomenclature, uric acid will appear as 2.6.8-trioxypurine, whilst xanthine and adenine (p. 387) are 2.6-dioxypurine and 6-aminopurine respectively.



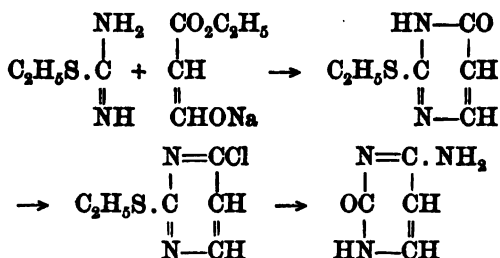
Uracil and its Derivatives. Before discussing the synthesis of uric acid reference must be made to a group of ureides which, like those already mentioned, appear to play an interesting rôle in animal metabolism.¹ The name *uracil* was given by Behrend to the simplest member of this special group. Though the compound itself has only recently been prepared, several of its derivatives have

¹ Burian has recently demonstrated the formation of uracil derivatives from purine bases, when the latter are treated with strong sulphuric acid in the presence of sugar.

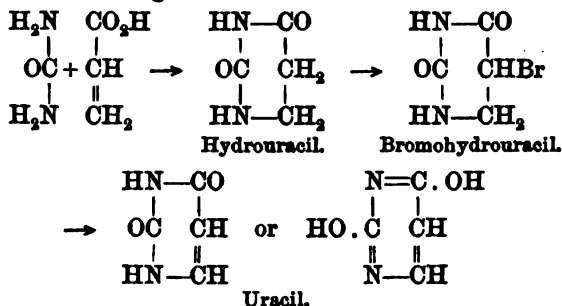
long been known and were isolated by Kossel and his pupils from the products of hydrolysis of nucleic acids (p. 421). Among these are *thymine* (5-methyl-uracil¹) and *cytosine* (6-amino-uracil).



Both compounds have been synthesised, the former by Behrend from α -methyl acrylic acid by a series of reactions similar to those used in the synthesis of uracil (see below), and the latter by Wheeler and Johnson² from ethyl pseudothiurea and sodium formylacetic ester. These two substances condense with the formation of 2-ethylmercapto-6-oxypyrimidine, which, with phosphorus pentachloride, yields a chlorine derivative. By the action of ammonia, the chlorine is replaced by the amino group, and, on hydrolysis with hydrobromic acid, cytosine is formed.



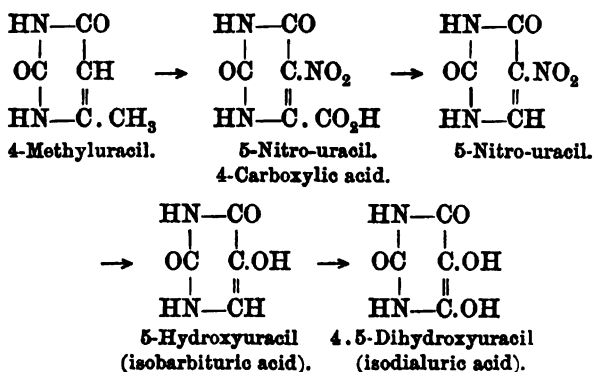
Uracil itself was first prepared by Fischer and Roeder³ by heating urea and acrylic acid to 210°, and the product, *hydrouracil*, was then brominated. When treated with pyridine, *bromohydrouracil* loses hydrogen bromide and gives uracil.



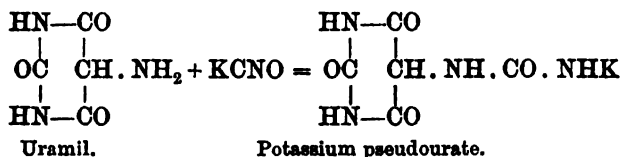
¹ The numbering of the atoms in uracil derivatives follows the order adopted in the case of uric acid.

² *Amer. Chem. J.*, 1908, 29, 492.

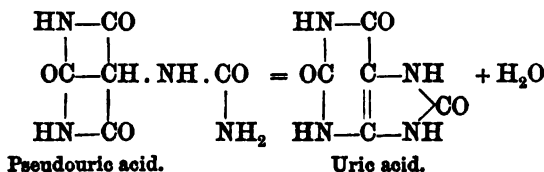
³ *Ber.*, 1901, 24, 8751.



E. Fischer's Synthesis. The starting-point of Fischer's synthesis¹ is pseudouric acid, the compound which many years before Liebig and Wöhler² attempted in vain to prepare with the object of converting it into uric acid. Baeyer and Schlieper³ were more successful, and obtained it in the form of the potassium salt by boiling uramil with a solution of potassium cyanate, from which pseudouric acid was then liberated.



Pseudouric acid differs in composition from uric acid by one molecule of water, but the early attempts to remove this molecule of water and convert pseudouric into uric acid failed. In Fischer's hands the operation was not only successful, but the process has served with little modification for the synthesis of other members of the purine group. The method which Fischer adopted was to boil pseudouric acid with hydrochloric acid.



The synthesis involves the preparation of uramil, which, as we have seen, may be obtained from barbituric acid through violuric acid

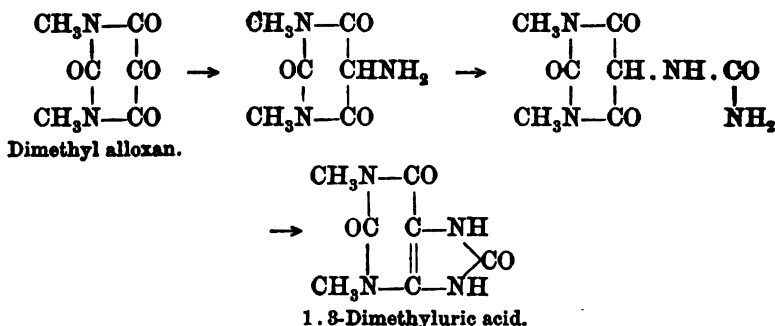
¹ *Ber.*, 1897, 30, 559.

² *Annalen*, 1838, 26, 241.

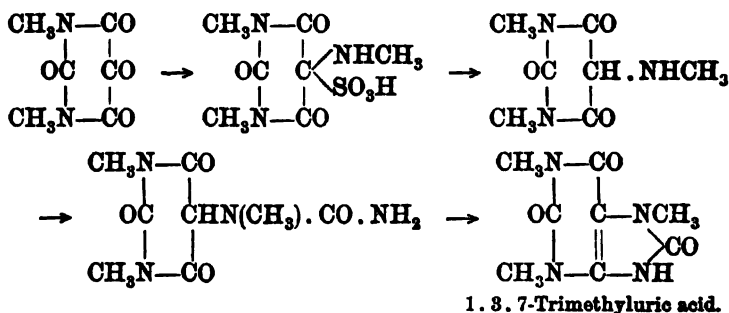
³ *Annalen*, 1868, 127, 8.

and also from alloxan through thionuric acid (p. 369). But the production of barbituric acid necessitates that of malonic acid, whilst alloxan is derived from barbituric acid or from uric acid itself. Thus, the synthesis depends in the first instance on the production of malonic acid.

The above synthetic method has been successfully applied by Fischer to the production of various alkyl derivatives of uric acid and, indirectly, to that of many of the xanthine bases, such as theobromine, theophylline, caffeine, &c. For example, mono- and di-alkyluric acids have been prepared from mono- and di-alkyl alloxans, which are converted into the corresponding uramils, pseudouric and uric acids. Thus, dimethyl alloxan yields 1.3-dimethyluric acid.



Moreover, it is possible to introduce a methyl group into position 7 by using methylamine sulphite in place of ammonium sulphite. 1.8.7-Trimethyluric acid (hydroxycaffeine) may be synthesised from dimethyl alloxan in this way:



W. Traube's Synthesis. Another synthetic method for the preparation of uric acid is described by W. Traube.¹ In this case the

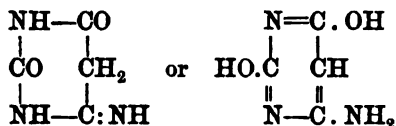
¹ Ber., 1900, 33, 1871, 8035.

starting-point is either cyanacetic acid or its ester. Cyanacetic acid and urea in presence of phosphorus oxychloride form cyanacetyl urea,



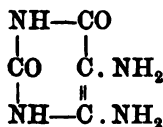
Cyanacetyl urea.

which by the action of alkalis is converted into 4-amino 2, 6-dioxypyrimidine.



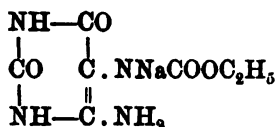
4-Amino-2, 6-dioxypyrimidine.

Nitrous acid then replaces the hydrogen of the methylene group by an isonitroso group, and the latter, on reduction with ammonium sulphide, is converted into an amino group, yielding the following compound:

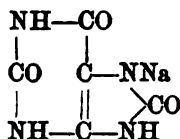


4, 5-Diamino-2, 6-dioxypyrimidine.

By the action of chloroformic ester a urethane is produced, which forms a sodium salt.



When the sodium salt is heated, alcohol is eliminated and sodium urate is formed.



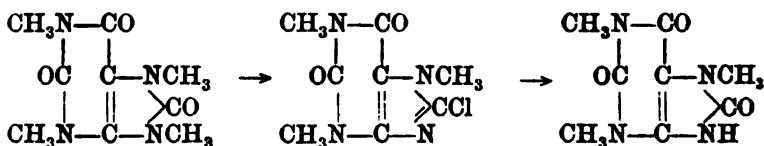
A similar method has been applied to the synthesis of xanthine, guanine, and similar compounds, to which reference is made on p. 888.

The Alkyluric Acids. In addition to the methyluric acids which may be prepared by Fischer's synthetic method already described, a number of these compounds have been obtained by the direct methylation of uric acid. The process is carried out by heating the

lead or silver salt with methyl iodide, or, more conveniently, by shaking up uric acid with methyl iodide in the presence of dilute caustic soda. The positions which the methyl groups assume depend to some extent upon the method of methylation and the temperature employed. The following methyluric acids have been obtained by the direct methylation of uric acid¹:

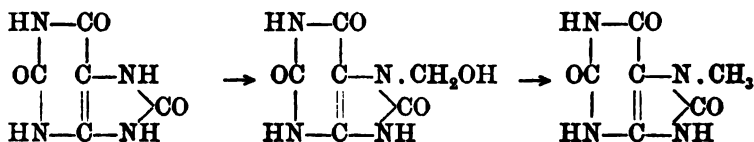
3-Methyluric acid.	1.3-Dimethyluric acid.	1.8.7-Trimethyluric acid.
9-Methyluric acid.	8.9-Dimethyluric acid.	8.7.9-Trimethyluric acid.
	7.9-Dimethyluric acid.	1.8.7.9-Tetramethyluric acid.

By the methylation of alkyluric acids of known constitution, prepared synthetically by Fischer's method, it has been possible to prepare some additional methyluric acids. In some cases a process of *demethylation* has been successfully employed. For example, if tetramethyluric acid—the product of the complete methylation of uric acid—be heated with phosphorus oxychloride, the methyl group in position 9 is detached, and at the same time the oxygen atom in position 8 is replaced by chlorine.



The 1.8.7-trimethyl-8-chloropurine produced in this way can be converted into 1.8.7-trimethyluric acid by alkalis, or may be used directly for other syntheses (cp. synthesis of caffeine, p. 385).

An additional method of preparation of methyluric acids consists in the reduction of the hydroxymethylene derivatives of uric acid, which are produced by the action of formaldehyde upon alkaline urates. For example, 7-methyluric acid is formed by the reduction of the compound produced by the interaction of formaldehyde and uric acid²:

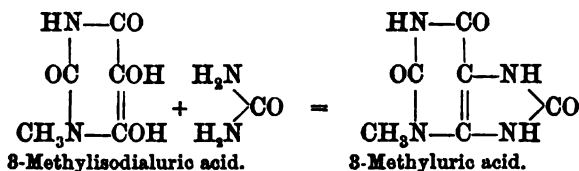


It is a curious fact that, in addition to the four isomeric mono-methyluric acids, obtained by the replacement of each of the four

¹ Reference to the method of preparation and structure of all the methyluric acids will be found in Fischer's paper, *Ber.*, 1899, 32, 461.

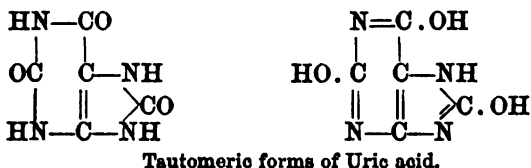
² *Chemisches Centralblatt*, 1900, i, p. 270.

hydrogen atoms of the imino groups in uric acid, two other monomethyluric acids are known, in both of which the methyl group is attached to nitrogen. Of these six monomethyluric acids, three appear to be produced by the replacement of the hydrogen of the imino group in position 3. They are known respectively as the α , δ , and ζ -methyluric acids. The α and ζ acids are prepared by the direct methylation of uric acid, the former by the usual method of alkylation, the latter by methylation in the presence of acetic acid. δ -Methyluric acid was obtained by v. Loeben¹ from 8-methylisodialuric acid by a similar method to that employed by Behrend and Roosen in their synthesis of uric acid (p. 874).



The δ and ζ acids are mutually interconvertible, since a mixture of both isomers results from heating either substance with hydrochloric acid.

The exact nature of the isomerism presented in the case of these three methyluric acids is still undetermined. The action of phosphorus chloride upon uric acid suggests that uric acid itself may react tautomerically,² thus:

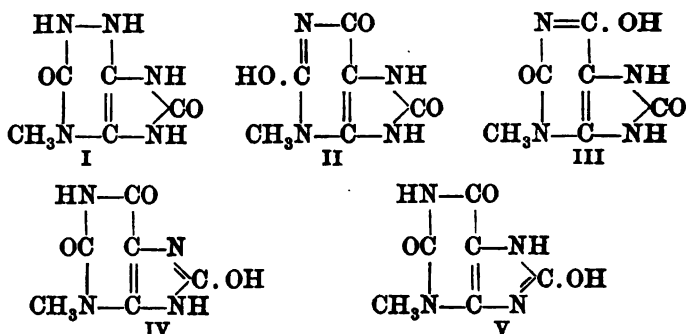


and it is possible that the isomerism of the methyluric acids is of a similar kind, although the stability of the substances is rather opposed to such a view.

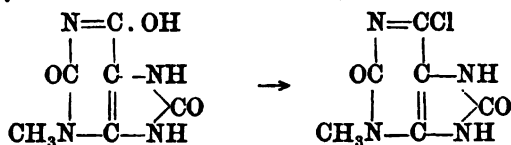
The assumption of this kind of tautomerism would imply the existence of a large number of isomers. Thus, in addition to the conventional lactam formula (I) for 8-methyluric acid, four other formulæ (II-V) may be deduced, which contain one lactim grouping, whilst the existence of two lactim groupings would allow of the existence of four more.

¹ v. Loeben, *Annalen*, 1897, 298, 181.

² The study of the absorption spectra lends support to the view that the purine compounds exhibit tautomerism, W. N. Hartley, *Trans. Chem. Soc.*, 1905, 87, 1796.

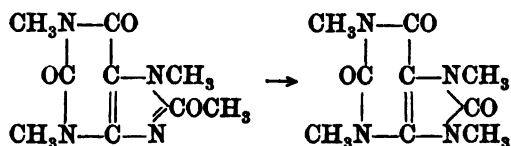


Of the three isomeric 8-methyluric acids, only the ζ -acid is converted smoothly into 8-methyl-2,8-dioxy-6-chloropurine, and this may be taken as an indication in favour of the subjoined formula for this substance :



Isomerism of a slightly different kind is found in the case of tetramethyluric acid and methoxycaffeine. The first is obtained by the action of methyl iodide on 1,8,7-trimethyluric acid in presence of an alkali, the second by its action on the silver salt of the acid, whilst both compounds are produced by the direct methylation of ζ -methyluric acid.

W. Wislicenus and Körber¹ have shown that methoxycaffeine passes on heating into tetramethyluric acid, a change which they represent as follows :



The Structure of the Xanthine Bases. One of the most notable developments in the history of the purine compounds belongs to the year 1881, when Emil Fischer² published his investigation on caffeine, theobromine, xanthine, and guanine, a memoir which still ranks as one of the many brilliant achievements of this distinguished

¹ *Ber.*, 1902, 35, 1991.

² *Ber.*, 1881, 14, 687, 1905; 1882, 15, 29; *Annalen*, 1882, 215, 258.

hemist. Xanthine is mainly a product of the animal organism and occurs combined in some nucleic acids, though it has also been detected in plant seedlings; theobromine is a constituent of cocoas (theobroma cacao); caffeine occurs in small quantities in tea and coffee; and guanine is associated with uric acid in guano and is a constituent of certain nucleic acids. Although of widely different origin, the close chemical relationship existing between them and uric acid had long been suspected. The composition and properties of xanthine and guanine are intimately related to those of uric acid.

Uric Acid $C_5H_4N_4O_3$

Xanthine $C_5H_4N_4O_2$

Guanine $C_5H_5N_5O$

Stenhouse¹ observed a reaction with caffeine which closely resembled the murexide test, whilst Strecker² succeeded in converting guanine into xanthine by the action of nitrous acid. In a subsequent paper Strecker³ explained the relationship of caffeine, theobromine, and xanthine by representing caffeine as trimethylxanthine and theobromine as dimethylxanthine. Though unsuccessful in methylating xanthine, he so far confirmed his views as to convert theobromine into caffeine by the action of methyl iodide upon the silver salt. So much was known when Fischer⁴ began his investigations. His first attack was directed against the caffeine molecule, which, as he anticipated, yielded more readily than the other compounds to the disintegrating action of reagents.

Caffeine, $C_8H_{10}N_4O_2$, on oxidation with chlorine water breaks up into equal molecules of dimethylalloxan and monomethylurea, and thus nine of the ten hydrogen atoms are present as methyl groups. With chlorine and bromine caffeine yields a monochloro- and monobromo-substitution product. By the action of alcoholic ammonia on the latter, the halogen is exchanged for an amino group; with alcoholic potash, for an ethoxyl group. The latter, on warming with dilute hydrochloric acid, yields hydroxycaffeine, which has since been identified as 1.3.7-trimethyluric acid. Hydroxycaffeine forms an additive compound with two atoms of bromine, yielding a dibromohydroxycaffeine, in which the bromine can be replaced by two ethoxyl groups by means of alcohol. The following formulae indicate the relation of the above series of compounds:

¹ *Annalen*, 1843, 45, 366; 46, 227.

³ *Annalen*, 1861, 118, 170.

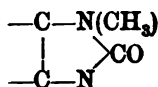
² *Annalen*, 1859, 108, 141.

⁴ *Annalen*, 1882, 215, 258.

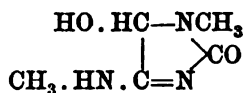
Caffeine	$C_8(NCH_3)_3O_2N$
Chlorocaffeine	$C_8Cl(NCH_3)_3O_2N$
Aminocaffeine	$C_8(NH_2)(NCH_3)_3O_2N$
Hydroxycaffeine	$C_8(OH)(NCH_3)_3O_2N$
Dibromohydroxycaffeine	$C_8(OH)(NCH_3)_3O_2NBr_2$
Diethoxyhydroxycaffeine	$C_8(OH)(NCH_3)_3O_2N(OC_2H_5)_2$

As the constitution of caffeine has been recently established by a simple and direct synthesis, and received in consequence a slightly different interpretation from the one originally attached to it by Fischer, the nature of the degradation products of the caffeine molecule, upon which the structure formerly depended, has lost something of its interest and value. The subject will therefore be treated quite shortly.

The decomposition of caffeine into dimethylalloxan and methyl urea indicates an atomic framework similar to that of uric acid. It also determines the positions of two methyl groups and one oxygen atom, and there is probably a double bond. Positions have therefore to be assigned to the third methyl group, one oxygen and one hydrogen atom. When diethoxyhydroxy-caffeine is boiled with hydrochloric acid it breaks up into methylamine, alcohol, and *apocaffeine*. Boiled with water, apocaffeine is in turn resolved into carbon dioxide and *caffuric acid*, and finally, caffuric acid can be hydrolysed into mesoxalic acid, methylamine, and methyl urea. By the action of hydrogen iodide on caffuric acid, *hydrocaffuric acid* is formed, which breaks up, on boiling with baryta, into methylamine, carbon dioxide, and methylhydantoin. Methylhydantoin contains the following atomic skeleton:

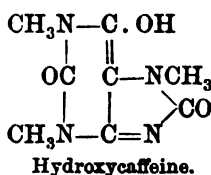
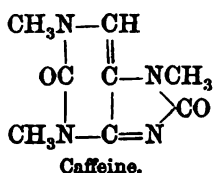


By the action of hydrochloric acid on diethoxyhydroxycaffeine, in addition to apocaffeine, *hypocaffeine* is formed, which is decomposed by bases into *caffoline* and carbon dioxide. As caffoline is converted on oxidation into dimethyloxamide, it probably possesses the following formula:

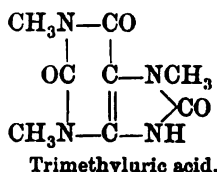
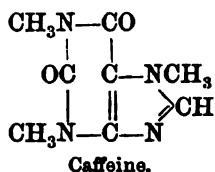


Assuming methylhydantoin and caffoline to represent the iminazole nucleus, an assumption which is justified by the relative

positions of the methylamino groups, Fischer represented caffeine and hydroxycaffeine by the following formulae :



The subsequent discovery that hydroxycaffeine was identical with trimethyluric acid, and yielded by further methylation with methyl iodide and potash, tetramethyluric acid, led to the adoption of the formula proposed by Medicus, for it is clear that tetramethyluric acid could not be derived from a substance possessing the formula originally assigned by Fischer.

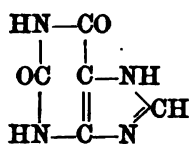


Fischer observed that xanthine, on oxidation with potassium chlorate and hydrochloric acid, was converted into alloxan and urea, whilst, on heating xanthine with hydrochloric acid at 190° , it was resolved into glycocholl, ammonia, and carbon dioxide. Both of these reactions clearly established the close relation existing between xanthine and uric acid, and the further observation that theobromine was formed by the action of methyl iodide upon the lead salt of xanthine established its connection with theobromine and caffeine.

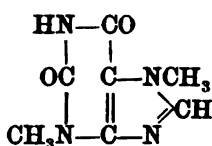
The constitution of theobromine is deduced from its conversion into caffeine on methylation, and by the fact that it yields methylalloxan and methylurea upon oxidation; further, that bromotheobromine is converted with potash into hydroxytheobromine, which has been identified as 8.7-dimethyluric acid.

Strecker's earlier discovery, that guanine can be transformed by nitrous acid into xanthine on the one hand and oxidised to guanidine on the other, determined the structure of guanine as an amino xanthine. The accepted formulae of these compounds are those originally assigned to them by Medicus.¹

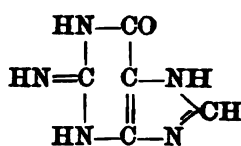
¹ *Annalen*, 1875, 175, 236.



Xanthine.



Theobromine.



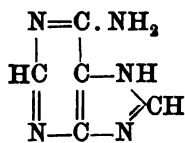
Guanine.

The above are not the only xanthine derivatives which occur in nature. Since Fischer's paper appeared new methyl xanthines have been brought to light. The following table contains a list of these compounds, their sources and their structure. Those which occur in urine are probably derived from the breaking down of caffeine.

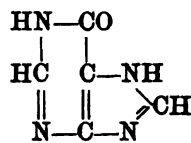
Natural Xanthine Bases.

<i>Name.</i>	<i>Synonym.</i>	<i>Occurrences.</i>
Xanthine	—	Animal tissues
1-Methylxanthine	—	Urine
7-Methylxanthine	Heteroxanthine	Urine
1.8-Dimethylxanthine	Theophylline	Tea
1.7-Dimethylxanthine	Paraxanthine	Urine
8.7-Dimethylxanthine	Theobromine	Cocoa
1.8.7-Trimethylxanthine	Caffeine	Tea, coffee, kola, &c.

In addition to the above, *hypoxanthine* and *adenine*, though not strictly xanthine derivatives, may be referred to as accompanying guanine and xanthine in the products of hydrolysis of nucleic acids. They are closely related to one another, for adenine is converted into hypoxanthine by the action of nitrous acid. Hypoxanthine is 6-oxypurine and adenine, the corresponding amino-derivative.



Adenine.

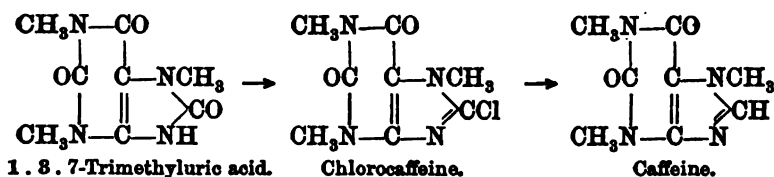


Hypoxanthine.

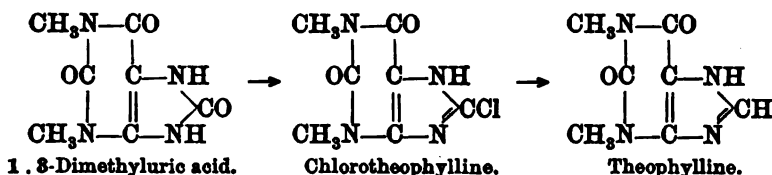
Synthesis of the Xanthine Bases. Having established the constitution of the xanthine bases as reduction products of uric acid and the methyl uric acids, the question arises, how can the syntheses of these different products be effected? Uric acid might be reduced to xanthine and the xanthine methylated, or uric acid might be converted into monomethyluric acid, then reduced to monomethyl xanthine and further methylated; or finally, the di- and tri-methyluric acids might be first prepared, and then reduced to the corresponding di- and tri-methyl xanthines. All three methods have been

utilized in turn by Fischer and carried to a successful issue; and since the process is similar in each case, one or two examples may suffice by way of illustration.

When 1.8.7-trimethyluric acid is heated with a mixture of pentachloride and oxychloride of phosphorus, it yields chlorocaffeine. Tetramethyluric acid yields the same product with the elimination of a methyl group in the form of methyl chloride. Chlorocaffeine is then reduced with strong hydriodic acid to caffeine.¹



1.8-Dimethyluric acid behaves similarly and forms theophylline.



This process cannot, however, be applied to uric acid in order to obtain xanthine or to 8- or 7-monomethyl- or to 8.7-dimethyluric acid, which might lead to the synthesis of theobromine; because in the first case the substance is destroyed and in the other cases the chlorine atom replaces the wrong oxygen atom, i.e. instead of replacing it in position 8, which is essential to the success of the operation, it enters position 6.

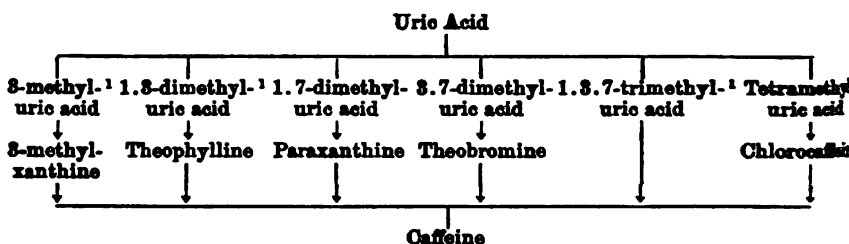
The happy idea of employing phosphorus oxychloride alone, in place of the mixture of pentachloride and oxychloride, has overcome this unforeseen difficulty and given a fortunate turn to the investigation.

By this modification 8.7-dimethyluric acid may be made to yield chlorotheobromine; or better still, 8-methyluric acid, which can be obtained by the direct methylation of uric acid, may be converted into 8-methyl-8-chloroxanthine. The latter can either be methylated

¹ The direct reduction of the methyluric acids to xanthine bases has never been effected by chemical reagents. Electrolytic methods, which have been investigated by Tafel, have shown that it is the oxygen of the carbonyl group in position 6 which is replaced by hydrogen. *Ber.*, 1901, 34, 279.

with methyl iodide in presence of caustic potash so as to give chlorotheobromine and, by methylation, chlorocaffeine, and then reduced, or first reduced to 8-methylxanthine and then methylated. As a rule, however, the methylation of the chlorine compound is more easily effected than that of the reduced product. Paraxanthine (1.7-dimethylxanthine) may be obtained from 1.7-dimethyluric acid, and, in a similar manner, converted by methylation into caffeine.

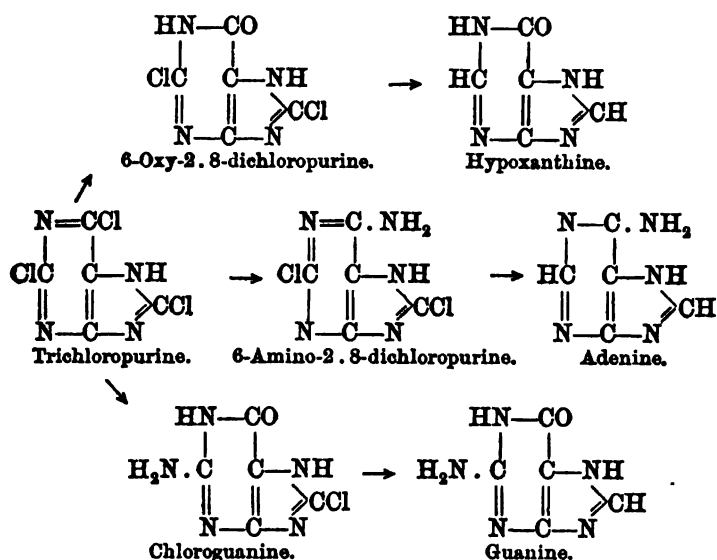
The following scheme will indicate the various directions in which the synthesis of caffeine has been accomplished.



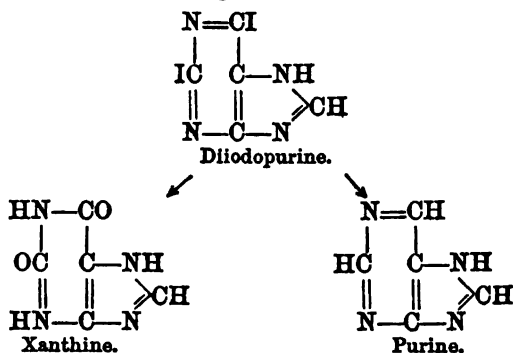
Heteroxanthine (7-methylxanthine) has been obtained by the action of phosphorus oxychloride on theobromine, which, by the elimination of one methyl group, forms 7-methyldichloropurine. By boiling this substance with hydrochloric acid, 7-methylxanthine is formed. Xanthine cannot be prepared from uric acid in so direct and simple a manner as the above, even when phosphorus oxychloride alone is used, for the first product, obtained in this way, is 8-oxy-2.6-dichloropurine; but by the action of a large excess of phosphorus oxychloride, uric acid may be made to part with its last atom of oxygen. Trichloropurine is then produced, and this compound has served for the synthesis of xanthine, its nearly related derivatives, hypoxanthine, adenine, and guanine, and finally, purine, the parent substance of the whole group.

When trichloropurine is treated with aqueous potash it yields 6-oxy-2.8-dichloropurine. The latter compound may be directly reduced with hydriodic acid to hypoxanthine, or converted with alcoholic ammonia into chloroguanine, which on reduction forms guanine. Aqueous ammonia converts trichloropurine into 6-amino-2.8-dichloropurine, which yields adenine on reduction.

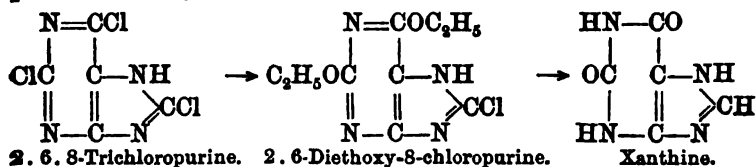
¹ These alkyluric acids are formed by the direct methylation of uric acid.



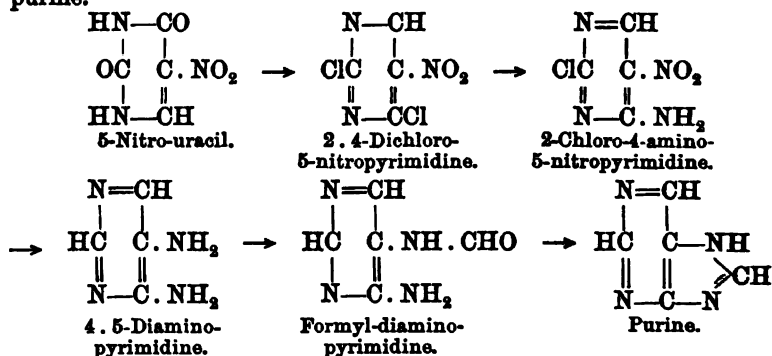
With strong hydriodic acid, trichloropurine is further converted into diiodopurine, which yields, with hydrochloric acid, xanthine, and with zinc dust and water, purine.



An alternative method for the synthesis of xanthine from 2:6:8-trichloropurine is to convert that substance by the action of sodium ethoxide into 2,6-diethoxy-8-chloropurine, and then to reduce the product with hydriodic acid.

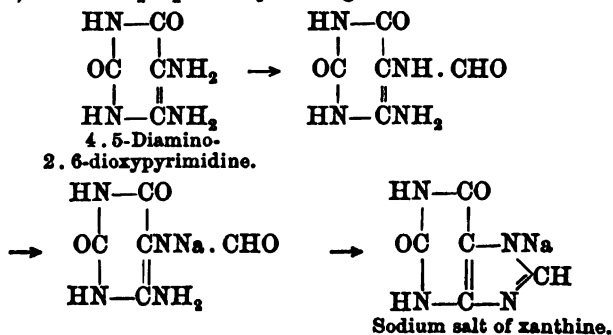


The direct synthesis of purine has recently been carried out by Issy.¹ The starting-point is 5-nitro-uracil, the preparation of which has already been described in connection with the synthesis of uric acid by Behrend and Roosen (p. 874). 2-Nitro-uracil, on being heated under pressure with phosphorus oxychloride, is converted into 2,4-dichloronitropyrimidine, which, on treatment with ammonia, loses one chlorine atom and passes into 2-chloro-4-amino-5-nitropyrimidine. On reduction with hydriodic acid, 4,5-diaminopyrimidine is produced, which is then converted into the formyl derivative. The latter substance, when heated to 210°, loses the elements of water and yields purine.



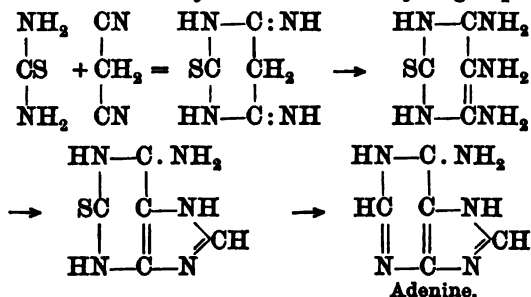
Purine, although neutral to litmus, forms well characterized salts, and shows surprising stability towards oxidising agents.

Traube's Synthesis of Xanthine Bases. This method closely resembles Traube's synthesis of uric acid (p. 876). Cyanacetylurea is converted, as before, into 4-amino-2,6-dioxypyrimidine; this substance is acted upon with nitrous acid, and the resulting isonitroso compound reduced to 4,5-diamino-2,6-dioxypyrimidine. Xanthine is obtained from the latter substance by heating the sodium salt of its formyl derivative, which is prepared by boiling with formic acid.

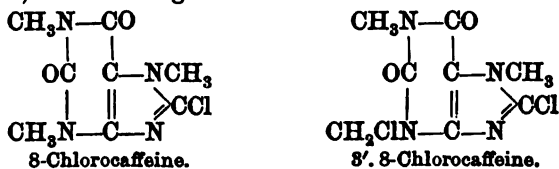


¹ Ber., 1906, 39, 250.

The method has been very widely applied to the synthesis of many other members of the purine group. Thus, if cyanacetylguanidine be substituted for cyanacetylurea, the final product will be guanine, whilst with mono- and dimethyl-cyanacetyl ureas, prepared by condensation of monomethyl- and dimethyl-urea with cyanacetic ester, the products will be 8-methylxanthine and 1,8-dimethylxanthine respectively. Since 8-methylxanthine, on methylation, yields both theobromine and caffeine, it is possible to employ this method for the commercial preparation of these substances. A further extension of the method¹ has led to the synthesis of hypoxanthine and adenine. If thiourea is used as the starting material, and submitted to a similar series of changes to those described above, 2-thio-6-oxypurine will result. On oxidising the latter with dilute nitric acid, hypoxanthine is formed by the elimination of an atom of sulphur. Adenine is obtained by a slightly different series of changes. Thiourea undergoes condensation with methylene cyanide, forming a thio-pyrimidine derivative, which is then converted into a purine compound by the methods employed in the previous syntheses. In the final reaction the sulphur is eliminated by oxidation with hydrogen peroxide.

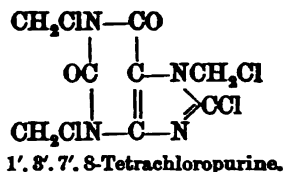
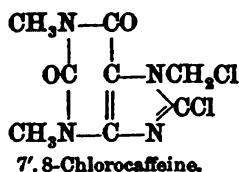


It is of interest to note that whilst caffeine can be prepared by the methylation of various xanthine bases, it is possible to effect the reverse change and to obtain many of the xanthine bases from caffeine by a process of *de*-methylation.² By the regulated action of phosphorus pentachloride or of chlorine dissolved in phosphorus oxychloride, the following substances are formed:



¹ *Annalen*, 1904, 331, 64.

² Fischer and Ach, *Ber.*, 1906, 39, 428.



It will be seen that chlorine first replaces the hydrogen in position 8, but, on further chlorination, the halogen enters the methyl groups. The chloromethyl groups are easily removed by heating with water, with the liberation of formaldehyde and hydrochloric acid. By this means the above compounds are converted into 8-chloroparaxanthine, 8-chlorotheophylline, and 8-chloroxanthine, which may be reduced to paraxanthine, theophylline, and xanthine respectively.

Heteroxanthine has also been prepared by a similar series of changes.

The Formation of Uric Acid in the Body. The relative amount of uric acid excreted varies enormously in different animal species. It forms the greater part of the nitrogenous constituents of the excreta of birds and reptiles, whilst in most mammals, including man, the proportion is only about 2 per cent. The origin of the uric acid in the two cases is entirely different. In the case of birds, ammonia or urea is converted into uric acid by the liver, and there is reason to believe that ammonium lactate is an intermediate product in the reaction. No such conversion of urea into uric acid occurs with mammals, but, on the contrary, the reverse change takes place, and uric acid, taken into the body, is mainly converted into urea. This power of destroying uric acid is generally ascribed to an enzyme in the liver—the so-called *uricolytic enzyme*. For reasons which are unknown this destruction of uric acid is never complete, so that a certain proportion of the uric acid present at any time in the body escapes by way of the urine. It is found that the uric acid present in the urine of mammals is derived from three sources. The use of certain substances as food, such as thymus, pancreas, and liver, which are rich in nucleo-proteides, is found to give rise to an increased uric acid excretion. The nucleo-proteides contain one or more of the purine bases, xanthine, guanine, hypoxanthine or adenine in combination, and these bases are converted into uric acid by the joint agency of the enzymes adenase, guanase, and xanthine oxidase (see p. 850). Only a portion of the uric acid so formed is eventually found in the urine. The term 'exogenous uric acid' has been employed to distinguish the uric acid directly

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derived from food from that produced in other ways. Since uric acid is excreted during prolonged starvation, or when the diet is free from purine bases, it is necessary to assume that at least part of the uric acid normally excreted is derived from the metabolism of the tissues and is independent of the food-supply. The term 'endogenous uric acid' is applied to uric acid which originates in this way, and may arise from the nucleo-proteides of disintegrated cells. Since nucleo-proteides taken in as food yield some part of their purine bases in the form of uric acid, it is natural to suppose that the breaking down of the nucleo-proteides of degenerating body cells would also yield uric acid. That this is probably the case is inferred from the fact that conditions which cause a large increase in the production (and destruction) of nucleated leucocytes (such as follows the use of certain drugs and is seen in leucaemia and other diseases), result in an increased uric acid excretion.

A third source of uric acid is found in *purine bases produced in metabolism*. The important fact has recently been recognized that purine bases may be produced in normal cell metabolism. It has been shown that hypoxanthine is found in the muscles, and that the quantity is increased during activity. The hypoxanthine does not leave the muscle as such, but is converted into uric acid by the action of an oxidising enzyme. The mode of production of the hypoxanthine is unknown. It is certain that the synthesis of purine bases is readily carried out in the living cell, because nucleo-proteides containing purine bases are formed in the development of young animals, and the latter derive their nourishment from food which need contain no purine derivatives.

REFERENCES.

- Synthesen in der Puringruppe*, by E. Fischer: *Ber.*, 1899, 32, 486.
Vegetable Alkaloids, by A. Pictet, trans. by H. C. Biddle. Wiley, New York, 1904.

CHAPTER XI

THE PROTEINS

THE proteins embrace a large and ill-defined group of substances which are derived directly or indirectly from living matter. They form the chief constituents of the protoplasm of the majority of cells and enter into the composition of animal tissues and secretions. A knowledge of their structure is clearly of the greatest importance to biological science. But their study offers peculiar difficulties. They are colloidal, non-volatile substances, and consequently difficult to obtain in a state of purity. Moreover, they do not lend themselves to investigation by simple chemical methods. The early investigators who turned their attention to the better known but more complex proteins, apart from collecting a number of interesting empirical facts, obtained little insight into their real nature.

At a later period the simpler members of the group, such as the protamines, were examined with more success by Kossel and others. Still more recently the comprehensive study of the simplest constituents or constitutive fragments of the protein molecule which was carried out by Emil Fischer and his co-workers, has thrown a flood of light on the subject. These constituents consist mainly of amino acids, for which new methods of separation, identification, and synthesis have been devised, so that the structure of the majority of them is now well known. The knowledge gained by these investigations has clearly indicated the lines upon which the construction of the simpler members of the protein group may be accomplished, and although we are still ignorant of the constitution of even the simplest protein, the problem has lost something of the hopeless aspect that it formerly presented.

Before considering individual members of the protein group, it will be convenient to give a brief outline of the methods employed in their investigation. Animal and vegetable tissues and fluids must of necessity serve as the material for their preparation. The plan almost universally adopted consists in *precipitating* by various means the proteins contained in the aqueous extracts, prepared by digesting the tissues with dilute alkali, acid, or salt solutions.

A great number of substances have been employed as precipitants, of which the most important are ammonium sulphate, sodium chloride, sodium sulphate, zinc sulphate, magnesium sulphate or organic liquids, such as alcohol, ether, and acetone. Frequently a protein may be precipitated from an alkaline solution by acidifying with some weak acid like acetic or carbonic acid. All proteins are precipitated on complete saturation of the solution with ammonium sulphate, a reagent which usually produces less alteration in unstable substances than alcohol or other similar precipitants.

The various proteins differ widely in the relative ease with which they are precipitated by salts, and it has been found that systematic 'salting out' forms one of the best available means of purification. It has long been known that *oxyhaemoglobin* (p. 424) and certain of the vegetable proteins may be obtained in the form of well-defined crystals, and, more recently, other proteins such as egg- and serum-albumin have been obtained in crystalline form by salting out under special conditions. Even when crystalline the proteins may contain many impurities arising partly from their power of adsorption; nevertheless, by repeated precipitation or crystallization, a number have been isolated which are believed to be individual substances of definite composition.

The proteins contain carbon, hydrogen, nitrogen, and oxygen, and most of them sulphur and phosphorus in addition. The relative proportion of carbon, hydrogen, and nitrogen in the majority of typical proteins varies within small limits, as will be seen from the following average numbers: carbon, 52-55 per cent.; nitrogen, 16-18 per cent.; hydrogen, 6.5-7.5 per cent. The molecular weights of the proteins are extremely high, but in every case exact determinations are still wanting. From a consideration of the products of hydrolysis, it is concluded that the simple protamines have a molecular weight of some multiple of 2,000, while the assumption that the complicated protein, *haemoglobin* (approximately $C_{158}H_{123}O_{195}FeS_3$), contains only one atom of iron in the molecule, leads to a minimum molecular weight of about 16,600.¹ Similar numbers are obtained from calculations based upon the proportions in which carbonic oxide or oxygen combine with haemoglobin.

The employment of physical methods of molecular weight determination has not led to completely satisfactory results, but they at least confirm the enormously high estimates made on chemical grounds. By the use of the freezing-point method, a molecular

¹ *Zeit. physiol. Chem.*, 1889, 14, 289.

weight of about 14,000 has been assigned to egg-albumin. Careful direct measurements of osmotic pressure in solutions of certain proteins have been made by Waymouth Reid¹; but, with the exception of haemoglobin, negative results were uniformly obtained. Assuming the molecular weight of haemoglobin to be 16,600, as deduced from its iron-content, it is calculated that, if no dissociation in solution occurred, a 1 per cent. solution of the protein would give a pressure of 10.7 mm. of mercury at 15°. Since the observed pressures are only about one-third of this, the true molecular weight appears to be a multiple of the minimal number calculated from analysis. In this connection it is of interest to note that the appearance of solutions of haemoglobin, when examined in a special form of microscope of high power, resembles that of distilled water, and presents a marked contrast to the milky appearance of the pseudo-solutions of certain other proteins. It is therefore probable that haemoglobin, unlike most other proteins, forms a true solution in water.

Taking advantage of the fact that certain proteins, such as casein, act as polybasic acids and form neutral salts with alkalis which are ionised in solution, Sackur² has deduced molecular weights from electrical conductivity measurements. In the case of casein, the combining proportions of sodium hydrate and protein lead to an equivalent of 1,185 for the latter, whilst the conductivity measurements indicate that this number must be multiplied from four to six times to give the molecular weight.

The wide variations in the molecular weight, estimated by different methods, renders it impossible to place much reliance upon the numbers, but as the experimental errors in most cases tend to give low results, it is probably safe to assume that few proteins have a molecular weight of less than 10,000.

One of the most characteristic properties of the proteins is the curious transformation which most of them exhibit when their solutions are heated. At a certain definite temperature the protein undergoes coagulation, forming an insoluble clot, which does not redissolve on cooling. The exact temperature at which coagulation takes place varies with different proteins and is influenced by the reaction of the solution and by the presence or absence of salts. The clotted proteins are much more insoluble and generally less reactive substances than the parent proteins, and they cannot be reconverted into the original coagulable proteins.

¹ *Journ. of Physiol.*, 1904, 31, 488; 1905, 33, 12.

² *Hofmeisters Beiträge*, 1902, 3, 193.

The proteins can function both as acids and as bases. Some, such as casein, have pronounced acid properties, whilst others, such as the protamines, are strongly basic substances, but indications of both basic and acid nature may be found in all. The explanation of this phenomenon may be referred to the presence in the protein molecule of amino-acid groups, in which there is a balance between the basic-amino and acid-carboxyl groups. If a portion is warmed with dilute acid it is converted into 'acid-albumin', while on similar treatment with caustic alkali it is rapidly changed to an 'alkali albuminate'. The nature of the reactions taking place is still unknown, but the products of the action of acids and bases upon proteins show great variations in properties from the parent substances, and their aqueous solutions no longer undergo typical coagulation on heating.

Colour Reactions of the Proteins. A number of colour reactions have been described which were at one time believed to be characteristic of the proteins. It has, however, been found that most of these reactions are due to the presence of special amino-acid groups in the protein molecule, to which reference is made later.

The Biuret Reaction. A fine pink or violet colour is produced on the addition of an excess of caustic soda and a trace of copper sulphate to a solution containing proteins. This reaction is given by all proteins, as well as by proteoses, peptones (p. 409), and all except a few of the simplest synthetical polypeptides (p. 410), but the test fails with the free amino acids. The tint varies considerably, but is usually bluish-violet with proteins and pink with the peptones. In addition to the protein derivatives, already mentioned, certain other substances, including biuret, malonamide, and oxamide, give the reaction. Schiff¹ has attempted to correlate those substances which yield the biuret reaction with their structure, but his results are no longer accepted as entirely trustworthy. It is probable that the reaction in the case of the proteins is due to groups which result from the condensation of amino-acid molecules among themselves, and as the dipeptides and many tripeptides do not give a distinct reaction, several of these groups appear to be necessary.

The Xanthoproteic Reaction. On addition of concentrated nitric acid to a protein solution, followed by gentle warming, a deep yellow colour results which changes to orange on the addition of ammonia. The reaction is due to the production of coloured aromatic nitro compounds. It is given by nearly all proteins; for, with the

¹ *Ber.*, 1896, 29, 298; *Annalen*, 1897, 299, 286; 1901, 319, 800.

exception of the protamines, they all contain heterocyclic phenyl-alanine or tyrosine groups (p. 406).

Millon's Reaction. Almost all proteins, with the exception of gelatine and the protamines, contain tyrosine groups in their molecule, and hence give a red colour on warming with Millon's reagent (p. 407).

Adamkiewicz-Hopkins Reaction. A fine bluish-violet colour is produced on adding half a volume of concentrated sulphuric acid to a protein solution containing a trace of glyoxalic acid.¹ The production of the colour depends upon the presence of tryptophane groups (p. 406), and a positive reaction is therefore obtained with all proteins with the exception of gelatine and the protamines.²

Lead Sulphide Reaction. The majority of proteins contain sulphur in the form of cystine groups (p. 408) and give a black precipitate of lead sulphide on boiling with caustic soda and lead acetate solution.

Molisch Reaction. A violet colour is produced on adding strong sulphuric acid to a protein solution containing an alcoholic solution of α -naphthol. This reaction is given by all proteins which contain carbohydrate complexes and depends upon the production of furfural by the action of the mineral acid.

On account of their physical properties the proteins do not lend themselves readily to direct investigation. Their structure and composition, as far as they have been elucidated, have been arrived at almost exclusively from a study of their products of hydrolysis and of oxidation. Of these two methods hydrolysis has proved to be much the most fruitful, in fact, the modern chemistry of the proteins is mainly concerned with the products obtained by various methods of hydrolysis. The methods are of two kinds, either purely chemical, in which mineral acids, alkali, or superheated steam are employed, or biochemical, in which the proteins are resolved into simpler products by means of enzymes which normally occur in living organisms, particularly in the digestive tract of animals. The hydrolysis of the proteins by enzymes is effected at low temperatures and in the absence of more than traces of acid or alkali. As the reaction occurs in several fairly well-defined stages, it has been possible to obtain from the complex proteins a number of products, intermediate in character between the simple end-products of complete hydrolysis and the parent substance. The importance of this method can hardly be over-estimated, especially

¹ Ordinary glacial acetic acid usually contains traces of glyoxalic acid and was originally employed for this test in place of the pure acid.

² A protamine named cyclopterine, however, contains tryptophane groups, and consequently gives a positive reaction.

as the course of the reaction may be varied to some extent by the employment of different enzymes. The more important products of protein hydrolysis, arranged in order of their complexity, are proteoses, peptones (including simple polypeptides), and amino acids. The first two classes of compounds will be referred to at a later stage, after the simpler amino acids have been discussed.

The Amino Acids. If a protein, for example egg-albumin or casein, be completely hydrolysed by boiling with concentrated hydrochloric acid, a clear, dark-coloured solution is obtained which no longer gives the biuret reaction. The problem of separating and identifying the products has long taxed the chemists' ingenuity. As long ago as 1820 Braconnot obtained glycocoll and leucine from gelatine, and thirty years later Liebig found tyrosine among the decomposition products of horn. Leucine and tyrosine were then so frequently encountered that these two amino acids were thought to comprise the bulk of the protein decomposition products. With the employment of better methods, other amino acids, such as aspartic and glutamic acids, were added to the list, and a great advance was made in 1889 when Drechsel showed that a considerable proportion of the products of protein hydrolysis were strongly basic substances belonging to the class of diamino acids. Ten years later Mörner was able to demonstrate the wide distribution of the sulphur-containing amino acid, cystine, whilst an acid of an entirely new type—tryptophane, a derivative of indole—was isolated by Hopkins and Cole. The recent introduction by Fischer of improved methods for the separation of amino acids, based upon their conversion into volatile esters (which can be partially separated by fractional distillation *in vacuo*), has led to the recognition of the wide distribution of acids such as alanine, serine, and phenylalanine, which had only been previously detected in the products from a few proteins, and to the discovery of two cyclic acids of a new type, α -pyrrolidinecarboxylic acid and hydroxy-pyrrolidinecarboxylic acid.

Products of Protein Hydrolysis. The different kinds of amino-acids present in the products of protein decomposition may be classified as follows:

- Monobasic monamino acids
- Dibasic monamino acids
- Diamino acids
- Hydroxy- and thio-monamino acids
- Heterocyclic amino acids
- Aromatic amino acids.

The following table contains the chief amino acids which have been isolated from the products of protein hydrolysis.

Monobasic Monamino acids.

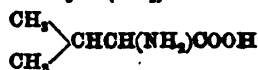
Glycocoll = aminoacetic acid



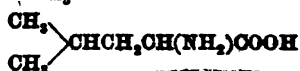
Alanine = α -aminopropionic acid



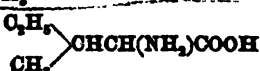
Valine = α -Aminoisovaleric acid



Leucine = α -aminoisobutylic acid



Isoleucine = secondary butyl α -aminoacetic acid

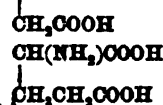


Dibasic Monamino acids.

Aspartic acid = aminosuccinic acid



Glutamic acid = aminoglutaric acid



Hydroxy- and Thio-amino acids.

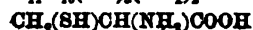
Serine = α -amino - β -hydroxypropionic acid



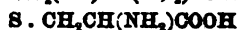
Trihydroxydiaminododecyl acid



Cysteine = α -amino - β -thiolactic acid



Cystine

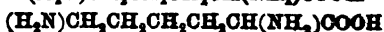


Diamino acids.

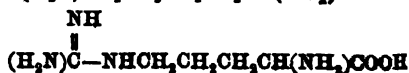
Ornithine = α - β -diaminovaleric acid



Lysine = α - ϵ -diaminocaproic acid

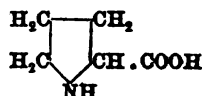


Arginine = α -amino - δ -guanidovaleric acid



Heterocyclic Amino acids.

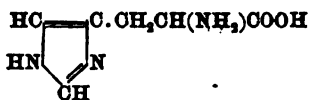
Proline = α -pyrrolidine carboxylic acid



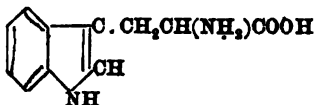
Oxyproline = hydroxypyrrolidine carboxylic acid



Histidine = α -amino - β -iminazole-
propionic acid



Tryptophane = indole-aminopropi-
onic acid



Aromatic Amino acids.

Phenylalanine = α -amino- β -phenyl-
propionic acid



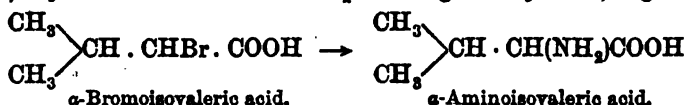
Tyrosine = α -amino - *p*-hydroxy-
phenyl-propionic acid



It will be seen from the table that there are about twenty different amino acids, the majority of which are commonly found among the products of hydrolysis of typical proteins, although their relative proportions vary considerably. Casein, for example, yields all the above-mentioned products of hydrolysis with the possible exception of glycocoll. These acids are all α -amino acids, and constitute practically the whole of the hydrolytic products of the proteins; a variable quantity of ammonia (0.4–5.0 per cent.) is usually set free, and, in the case of hydrolysis by acids, certain secondary decomposition products are commonly met with. The mode in which the different amino acids are united in the protein molecule will be considered at a later stage.

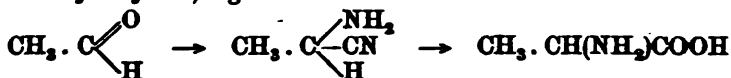
Monobasic Monamino Acids. The monobasic monamino acids form a large part of the products of hydrolysis of most proteins. That they serve as a source of energy available for the animal organism, naturally follows from the fact that they are produced in large quantities in the process of intestinal digestion of protein food. They are all crystalline, sweet-tasting substances which are soluble in water, but insoluble in alcohol and ether. They have a neutral reaction, but form well-defined crystalline salts with both acids and bases. With the exception of glycocoll they all contain asymmetric carbon atoms, and they are known in both racemic and active forms, one of the latter being present in protein decomposition products. All the amino acids of this group have long been known and their synthesis has been accomplished by means of the two following reactions:

(a) By the action of ammonia upon halogen fatty acids, e. g.



The α -bromo fatty acids, necessary for the synthesis, may be prepared by the ordinary methods of direct bromination, but in many cases better yields are obtained by brominating the corresponding alkylmalonic acid and then converting the product into a monobasic acid by distillation.¹

(b) By Strecker's method, which consists in combining an aldehyde with ammonia and hydrocyanic acid and hydrolysing the resulting amino-cyanhydrin, e.g.



Acetaldehyde.

Alanine.

The optically active acids are obtained from the racemic forms, in some cases by the actions of organisms; but more generally by a method which is due to E. Fischer.² It consists in the conversion of the amino acids into strongly acid benzoyl or formyl derivatives, which yield well-crystallized salts with alkaloids, capable of separation by fractional crystallization (p. 78). The optically active acyl derivatives yield the active amino acids on hydrolysis.

Dibasic Monamino Acids. Two dibasic monamino acids, aspartic and glutamic acids, are important constituents of many protein decomposition products. In the case of the proteins from wheat, the yield of glutamic acid may exceed 80 per cent. Aspartic and glutamic acids, as might be anticipated, are strongly acid substances which form well-defined metallic salts, but they still retain the power of combining with acids.

Inactive aspartic acid has been synthesised by heating fumaric acid with ammonia, and the *d*-acid, by acting upon *l*-bromo succinic acid with ammonia,³ whilst glutamic acid was obtained by the reduction of α -isonitrosoglutaric acid.⁴

The Diamino Acids. The diamino acids are strongly basic substances, which are among the most constant and characteristic products of protein hydrolysis. The first members were discovered by Drechsel, who isolated lysine and a substance which he named *lysatinine*. The latter was subsequently shown by Hedin to be a mixture of lysine with a base named *arginine*, which had previously been detected in lupine seedlings by E. Schulze. Somewhat later a third base *histidine* was independently discovered by Kossel and by Hedin, and for some time it was thought that this

¹ E. Fischer, *Ber.*, 1904, 37, 3062; 1906, 39, 851.

² *Ber.*, 1899, 32, 2451.

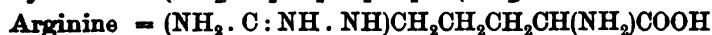
³ Fischer and Raake, *Ber.*, 1907, 40, 1051.

⁴ Wolff, *Annalen*, 1890, 260, 79.

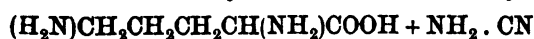
substance might be classified with lysine and arginine, but recent work has shown that it has an entirely different constitution (see p. 405). These three bases, lysine, arginine, and histidine, each contain six carbon atoms and are frequently spoken of as the *hexone* bases, but since the constitution of these substances has been ascertained the term seems scarcely suitable.

Arginine is perhaps the most widely distributed of the amino acids, and although the amount may be small, there is no protein which does not yield this substance on hydrolysis; thus *elastin*, a connective tissue protein, yields only 0.8 per cent., while as much as 90 per cent. is found in many protamines. It is completely resistant to the action of acids, but is easily decomposed by alkali or by an enzyme *arginase* yielding urea and a new diamino acid, *ornithine* (p. 352).

From the formulae of these substances it will be seen that they all contain an amino group in the α -position and a straight chain of five or six carbon atoms.



A clue to the constitution of ornithine and lysine was furnished by the observation of Ellinger,¹ who found that these substances are converted by the action of putrefactive organisms into tetramethylenediamine and pentamethylenediamine respectively, whilst the relation of arginine to ornithine was made clear by Schulze's² synthesis of the former substance by the direct addition of cyanamide to ornithine.



Ornithine.



The synthesis of ornithine and lysine offered considerable difficulties, but these have been successfully overcome by E. Fischer³ and later by Sørensen.⁴ Phthalimidopropylmalonic ester, which served as the starting-point for Fischer's synthesis of ornithine, was converted into phthalimido- α -bromovaleric acid by bromination; the bromine was then replaced by an amino group by means of

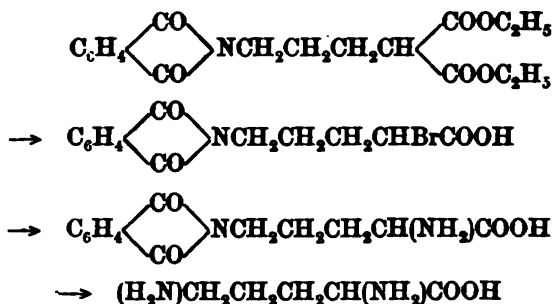
¹ *Zeit. physiol. Chem.*, 1900, 29, 834.

² *Ber.*, 1899, 32, 8191.

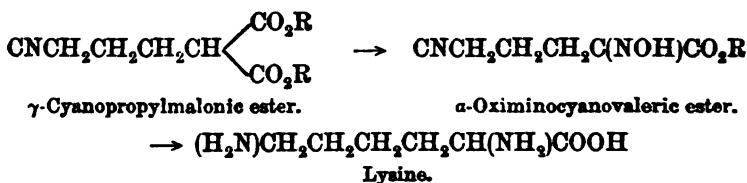
³ *Ber.*, 1901, 34, 454; 1902, 35, 3772.

⁴ *Compt. rend. trav. Laborat. Carlsberg*, 6.

ammonia, and the product gave inactive ornithine on removal of the phthalyl group by hydrolysis.



Fischer's synthesis of lysine depends upon the conversion by nitrous acid of γ -cyanopropylmalonic ester into an oximino derivative of a monobasic acid. This substance on reduction with sodium and alcohol yields α - ϵ -diaminocaproic acid (lysine).



Ornithine is not usually found among the products of hydrolysis of proteins by acids. Lysine, on the other hand, is a very general constituent of the hydrolytic products of proteins, and is absent only from certain protamines and from a few vegetable proteins such as zein (p. 420).

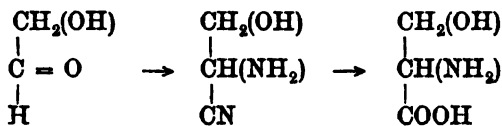
Ornithine, arginine, and lysine, like many other bases, are precipitated from acid solutions by means of phosphotungstic acid. The other amino-acids, with the exception of some of the heterocyclic acids (histidine and α -pyrrolidine-carboxylic acid), are not precipitated by this reagent, which is therefore used as a means of separation.¹

Hydroxy- and Thio-monamino Acids. The presence of serine (α -amino- β -hydroxypropionic acid) among the products of hydrolysis of the proteins found in raw silk, was observed as long ago as 1865 by Cramer,² but it is only within recent years that it has been recognized as a common protein constituent. Its isolation offers considerable difficulties, which are in part avoided by the employment of

¹ Methods for the approximate quantitative determination of lysine, arginine, and histidine, are given by Kossel and Kutscher, *Zeit. physiol. Chem.*, 1900, 31, 165.

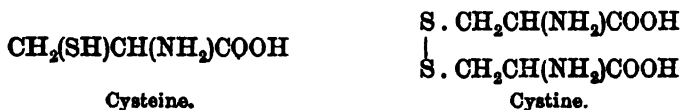
² *J. prakt. Chem.*, 1865, 96, 76.

Fischer's ester method of separation (p. 408). Serine contains an symmetric carbon atom, and proteins yield the laevo form. Its constitution follows from its conversion into glyceric acid by the action of nitrous acid, from its reduction to alanine by hydriodic acid, and from its synthesis which has been accomplished by Fischer and Leuchs,¹ and also by Erlenmeyer.² The two former obtained a small quantity of serine by the hydrolysis of the aminocyanhydrin derived from glycollic aldehyde.



Although it is likely that hydroxyamino acids constitute an important part of the fragments of the protein molecules, serine, diamino-trihydroxy-dodecylic acid and hydroxypyrrolidine carboxylic acid, are the only representatives of this class of substances which have so far been isolated.

The larger part of the sulphur of most proteins is found among the products of hydrolysis as cystine or cysteine. The latter substance is the sulphur analogue of serine, whilst cystine is the corresponding disulphide.³ Apparently cystine is the primary product, but it may be partly reduced to cysteine during hydrolysis. The same reduction is readily brought about by zinc and dilute sulphuric acid, while, on the other hand, cysteine dissolved in dilute ammonia, is readily oxidised by air to cystine.



Cysteine, unlike serine, is powerfully laevo-rotatory, although it is partially racemised in the process of hydrolysis. It is readily prepared from horn or hair, which may yield from seven to fourteen per cent.⁴ The racemic form has been obtained by Erlenmeyer, jun.,⁵ by methods similar to those which he employed in the synthesis

¹ Ber., 1904, 35, 3787; 1906, 39, 2942; 1907, 40, 1501.

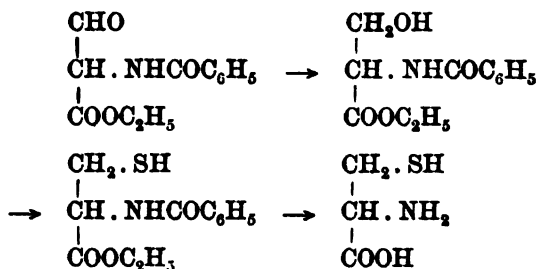
² Ber., 1904, 35, 3769.

³ According to Baumann's original formulae for cysteine and cystine, the nitrogen and sulphur atoms were attached to the same carbon atoms. The present formula is determined by the work of Friedmann, *Zeit. chem. Phys. u. Path.*, 1902, 2, 438, and Neuberg, *Ber.*, 1902, 35, 3161.

⁴ K. A. H. Mörner, *Zeit. physiol. Chem.*, 1899, 28, 599; 1901, 34, 207; 1904, 42, 347.

⁵ *Annalen*, 1904, 307, 236.

of serine. Ethylformyl hippurate, prepared by the condensation of formic and hippuric esters, forms, on reduction, the ester of benzoyl-serine, and this substance yields on treatment with phosphorus pentasulphide a thio-derivative, from which cysteine may be obtained on hydrolysis. Cysteine, as already mentioned, may be readily oxidised to cystine.



Cystine and cysteine are substances of considerable physiological importance, since many other compounds, such as hydrogen sulphide, methyl mercaptan, ethyl mercaptan, ethyl sulphide, taurine, and other substituted sulphuric acids, are obtained by their decomposition through the agency of living organisms.

Heterocyclic Amino Acids. α -Pyrrolidine carboxylic acid (proline) is the simplest member of this group of amino acids. It was discovered by Fischer¹ among the products of hydrolysis of casein and identified with the synthetical acid which shortly before had been obtained by Willstätter,² by the action of ammonia upon α - δ -dibromopropyl-malonic ester.

Further investigation has shown that this acid occurs among the decomposition products of a variety of proteins, including the protamines. It is not certain whether α -pyrrolidine carboxylic acid is a primary product of hydrolysis, for it might be derived from α -amino δ -hydroxyvaleric acid, which readily passes into pyrrolidine carboxylic acid on treatment with acids. This hydroxy acid has not, however, been detected among the products of protein decomposition.

α -Pyrrolidine carboxylic acid is readily soluble in alcohol, and can be partially separated by this solvent from most other amino acids. It is known in both the active and racemic forms.

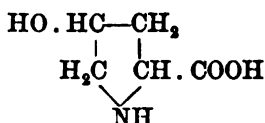
Shortly after the discovery of pyrrolidine carboxylic acid, Fischer found a hydroxy derivative of the same acid among the products of hydrolysis of gelatine.³ The isolation of the latter is a tedious and

¹ *Zeit. physiol. Chem.*, 1901, 33, 167; 1902, 35, 227.

² *Ber.*, 1900, 33, 1160.

³ *Ber.*, 1902, 35, 2660.

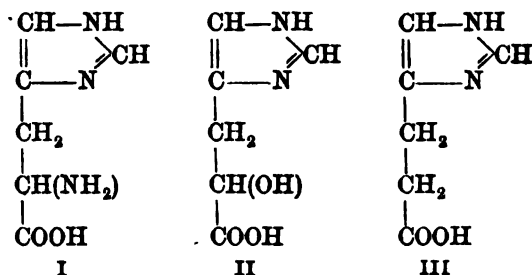
difficult process, and has only been accomplished in the case of a few proteins. It is a strongly laevorotatory substance, and on reduction is converted into pyrrolidine carboxylic acid. Two stereoisomeric hydroxypyrrolidine carboxylic acids, with the following structural formula,



have recently been synthesized by Leuchs,¹ and one of these probably corresponds to the racemic form of the optically active acid obtained by Fischer.

Histidine is an interesting amino acid which has been found among the products of hydrolysis of many different proteins. It was discovered by Kossel² among the decomposition products of a protamine named *sturine* (p. 416), and was obtained independently by Hedin³ from the products of hydrolysis of the more complex typical animal and vegetable proteins. The quantity is usually small, but in some proteins, such as globin, the yield may be as high as 10 per cent.

Until recently histidine was classified among the diamino acids, but it is now known to have little in common with these substances. Histidine is, in fact, an iminazole derivative which accounts for the formation of a red colouring matter when it is treated with alkaline solutions of diazonium salts (p. 422). The generally accepted formula for histidine (I) which was adopted by Pauly⁴, has received support from the experiments of Knoop and Windaus⁵, who showed that β -iminazole propionic acid (III) was formed by the reduction of the substance (II), obtained by the action of nitrous acid upon histidine.



¹ Ber., 1905, 38, 1987.

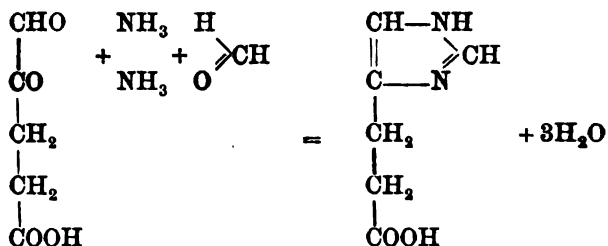
² Zeit. physiol. Chem., 1896, 22, 176.

³ Zeit. physiol. Chem., 1896, 22, 191.

⁴ Zeit. physiol. Chem., 1904, 42, 508.

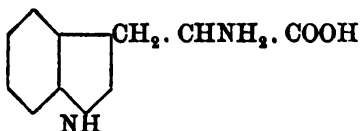
⁵ Beitr. z. Chem. Phys. u. Path., 1905, 7, 144.

Knoop and Windaus synthesized β -iminazole-propionic acid by condensing glyoxylpropionic acid with ammonia and formaldehyde.

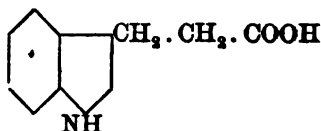


Tryptophane, which was first isolated from casein by Hopkins and Cole,¹ contains an indole nucleus, and therefore presents certain analogies with the aromatic as well as with the heterocyclic acids. Though one of the most constant constituents of the proteins, it is not found in most of the protamines nor in gelatine.

Some knowledge of the structure of tryptophane is derived from the fact that, on fusion with potash, it gives both skatole and indole, and a similar decomposition is brought about by putrefactive organisms which yield, in addition, indole-acetic acid and indole-propionic acid (II). Tryptophane has not yet been synthesized; but its reactions agree well with the following formula (I):



I. Tryptophane.



II. Indole-propionic acid.

That the amino group is probably in the α -position, follows from the observation of Hopkins, that optical activity disappears when tryptophane is converted into indole-acetic acid.

Tryptophane, either in the free state or when combined in the protein molecule, is readily detected by the deep violet-blue colour which it yields on treatment with strong sulphuric acid and a trace of glyoxylic acid. A violet colour results on the addition of a small quantity of chlorine or bromine to an acid solution of tryptophane.

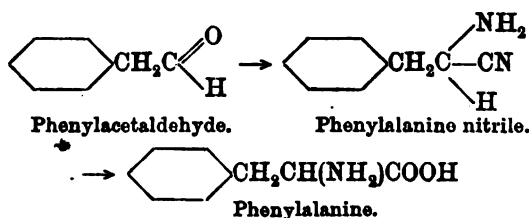
The Aromatic Amino Acids (Phenylalanine and Tyrosine). Phenylalanine (α -amino- β -phenylpropionic acid) was found by Schulze² more than twenty-five years ago in plant seedlings, and in the products of hydrolysis of seed proteins; but it is only within recent years, with the aid of the ester methods of isolation, that phenylalanine has been

¹ *Journ. of Physiol.*, 1901, 27, 418; 1908, 29, 451.

² E. Schulze and Bosshard, *Ber.*, 1881, 14, 1785; *Zeit. physiol. Chem.*, 1884, 9, 63.

recognized as a common constituent of the typical proteins. Phenylalanine in most respects resembles the aliphatic monamino acids. On oxidation with potassium bichromate and sulphuric acid it yields phenylacetaldehyde, which is readily detected by its hyacinth-like odour. It is interesting to note that phenylalanine under the influence of bacteria yields phenylethylamine, phenylacetic acid, and phenylpropionic acid, changes which closely resemble those sustained by tyrosine and tryptophane under similar conditions.

Phenylalanine was first synthesized by Erlenmeyer and Lipp¹ as follows: phenylacetaldehyde is converted into the nitrile of phenylalanine by the action of ammonia and hydrocyanic acid and yields phenylalanine on hydrolysis with acids.

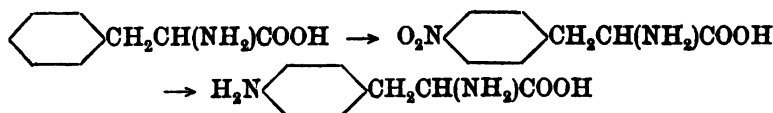


A more convenient synthesis from benzylmalonic acid has been described by Fischer,² who has also resolved the racemic acid into its optically active components.

Tyrosine (α -amino- β -hydroxyphenyl-propionic acid) was one of the earliest known protein derivatives, and, on account of the ease with which it may be detected, its presence has been established in almost all proteins with the exception of gelatine and some of the protamines.

Tyrosine is readily detected by Millon's reagent,³ which gives a red coloration or precipitate on warming. This reaction is due to the phenolic group and is shared by other phenols, but among the protein derivatives no substance other than tyrosine reacts in this manner. The test is directly applicable to proteins as well as to free tyrosine.

The synthesis of tyrosine has been accomplished by nitrating phenylalanine, reducing the resulting *para*-nitro derivative, and then replacing the amino group by hydroxyl by means of nitrous acid.



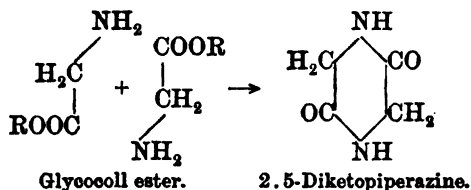
¹ Ber., 1882, 15, 1006.

² Ber., 1900, 33, 2833; 1904, 37, 3064.

³ A solution of mercuric nitrate containing nitrous acid.

Esters of the Amino Acids. The amino acid esters have acquired great importance, not only on account of their employment in the synthesis of *polypeptides* and other amino acid derivatives, but also owing to their great practical value as a means of separating the acids from mixtures produced by protein hydrolysis. The esters were originally prepared by the action of alkyl iodides upon the acids, but this method has a limited application and is no longer used. Curtius showed that the amino acids were readily converted into the hydrochlorides of their esters by the action of hydrochloric acid and alcohol, and in some cases the free esters were obtained from the salts by treatment with silver oxide. A more practical method for the isolation of most of the esters is that devised by Fischer,¹ who found that the crude hydrochlorides can be decomposed at a low temperature with caustic soda and may then be extracted by ether from the solution, after saturation with potassium carbonate. The free esters may be purified by distillation under low pressure.² Some amino acids, e.g. tyrosine, require special methods for the liberation of their esters, while in the case of the esters of histidine and the diamino acids it is impossible to effect purification by distillation.

The esters are strongly basic liquids, with a peculiarly unpleasant smell. They form crystalline salts with acids and are readily hydrolysed by water or alkalis. They are very reactive, unstable substances, and are converted into diketopiperazine derivatives on long standing, or better, by heating to 100°. Glycocoll ester, for example, is readily transformed into 2,5-diketopiperazine.



It is possible to effect a partial separation of the esters by fractional distillation. The investigation of the products of hydrolysis of the proteins, so far as it concerns the *mono*-amino acids, is accomplished by boiling the protein with strong hydrochloric acid, evaporating under diminished pressure, and then treating the residue with alcohol and hydrogen chloride. The free esters are extracted as described above and are then distilled *in vacuo*. The different

¹ Ber., 1901, 34, 438.

² E. Fischer, Ber., 1901, 34, 433.

fractions are then hydrolysed and examined for the corresponding amino acids.¹ The boiling-points of some of the more important amino acid esters are given in the following table:

<i>Ethyl Ester.</i>	<i>b. p.</i>	<i>Pressure in mm.</i>
Glycocoll	51.5°-52.5°	10
Alanine	48.5	10
<i>dl</i> -Aminoisovaleric acid	63.5	8
Leucine	83.5	12
<i>l</i> -Aspartic acid	126.5	11
<i>d</i> -Glutamic acid	139-140	10
<i>dl</i> -Phenylalanine	143	10

Proteoses and Peptones. The proteoses and peptones are substances formed by the partial hydrolysis of proteins, and their relation to the proteins may be compared to that existing between the di- and tri-saccharoses or the dextrans and starch. They are commonly prepared by the peptic digestion of proteins. After removal of any unchanged coagulable protein, the different proteoses are fractionally salted out with ammonium sulphate.² After complete saturation with ammonium sulphate the filtrate which contains the peptones is evaporated, freed as far as possible from ammonium sulphate, and the peptones precipitated with alcohol. As will be seen from the mode of preparation the proteoses and peptones are distinguished by their different solubilities in salt solutions. They may be further identified by the biuret test and the action of nitric acid. The proteoses give a reddish-violet biuret reaction, and are precipitated by dilute nitric acid in the cold, especially in presence of sodium chloride; the peptones give an intense pink biuret reaction, and are not precipitated by nitric acid nor by many protein precipitants.

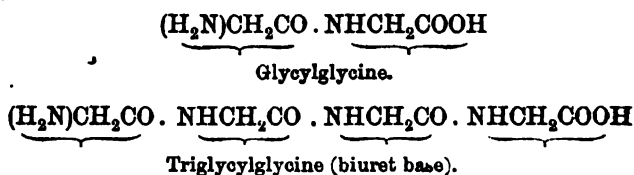
The peptones have a lower molecular weight than the proteoses, but exact determinations are in most cases still wanting. They are readily diffusible substances, and in this respect show a great contrast to the proteoses, which diffuse but slightly, and to the proteins, which are non-diffusible.

¹ The practical details of these operations will be found in papers by Fischer and others in the *Zeit. physiol. Chem.*, vol. 33, et seq.

² The proteoses according to Kühne's classification are divided into primary (protalbumose and hetero-albumose) and secondary proteoses, and it was believed that the primary proteoses on further hydrolysis were converted into secondary proteoses and eventually into peptones. The task of separating the different proteoses has been attempted by many chemists but cannot be referred to here. It is improbable that the substances obtained were chemical individuals.

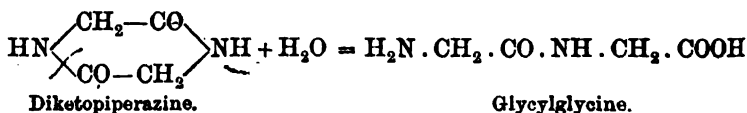
A great many different peptones have been described, but the methods employed for their isolation are such as to lead to the belief that most of them represent mixtures of closely related bodies rather than individual substances. Recently, however, Fischer¹ has been able to separate a peptone (very probably glycylalanine) from the products of hydrolysis of silk, and Levene and Beatty² have isolated the anhydride of glycylproline from the products of the tryptic digestion of gelatine. It can hardly be doubted that, if adequate methods were available, many similar compounds would be found. At present all the evidence tends to show that the peptones are derived from the condensation of comparatively few amino acid molecules. This view is strongly supported by the fact that Fischer has been able to unite a number of amino acid groups, forming compounds, known as *polypeptides*, which exhibit a certain similarity to the natural peptones.

Polypeptides. According to the number of amino acid groups present in the molecule these compounds are known as di-, tri-, tetra-, &c., peptides.³ The simplest of these peptides is the dipeptide, *glycylglycine*, formed by the union of two molecules of glycocoll, whilst the so-called *biuret base*, obtained by Curtius⁴, by the spontaneous decomposition of glycocoll ester, is an example of a simple tetra-peptide:



The following methods for the synthesis of these substances have been devised by E. Fischer:

(1) *The action of alkalis or acids upon derivatives of 2.5-diketopiperazine.* As already mentioned (p. 408) amino acid esters are changed by heat into derivatives of 2.5-diketopiperazine, and many of these substances are converted into polypeptides by partial hydrolysis.



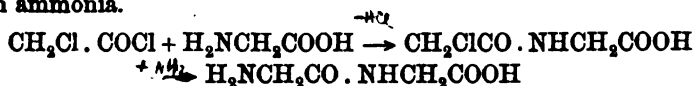
¹ Ber., 1908, 36, 2592; 1906, 29, 752.

² Ber., 1906, 39, 2060.

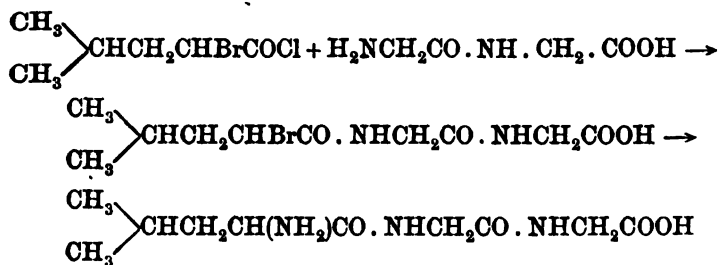
³ Ber., 1906, 39, 551.

⁴ Ber., 1904, 37, 1284.

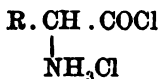
(2) *The action of ammonia upon the products of the reaction between acid chlorides of halogen fatty acids and amino acids or their esters.* This method has proved to be of the greatest service and renders possible the successive introduction of different amino acid radicals into a simple polypeptide or amino acid. For example, the product of the interaction of chloroacetylchloride and glycocoll yields glycylglycine with ammonia.



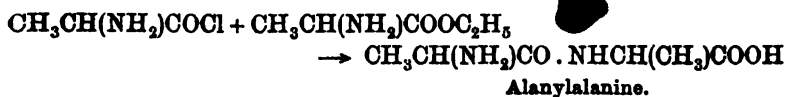
The glycylglycine may again be acted upon by another halogen acid chloride, the product again treated with ammonia, and the process repeated. Thus, glycylglycine may be converted into leucylglycylglycine by the use of α -bromisocaproylchloride.



(3) *From the acid chlorides of amino acids.* Methods for the preparation of the acid chlorides of the amino acids have only recently been discovered, but these substances promise to be of the greatest use in the synthesis of polypeptides. The acid chlorides are obtained in the form of hydrochlorides of the general formula

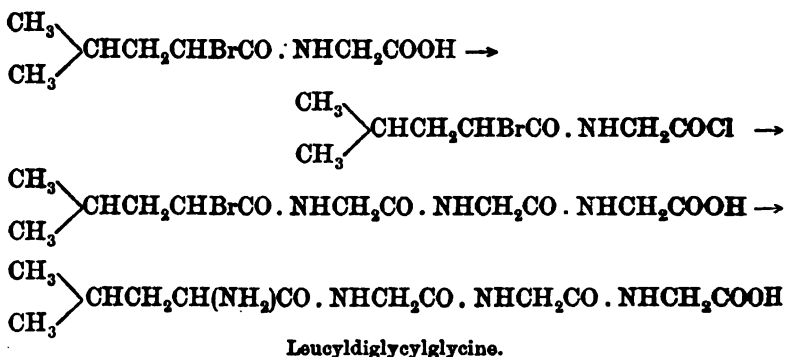


by the action of phosphorus pentachloride upon amino acids, using acetylchloride as solvent. When brought into contact with the esters of amino acids they yield the esters of dipeptides from which the free peptide is obtained by hydrolysis. Alanyl chloride and alanine ester give in this way alanylalanine:



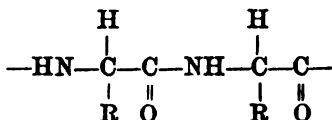
The same method serves for the preparation of the acid chlorides of some of the intermediate products used in the production of polypeptides. For example, α -bromisocaproylglycine, treated with

phosphorus pentachloride and acetylchloride, is converted into an acid chloride from which a number of polypeptides may be prepared. Thus, on condensation with glycylglycine ester it forms a product which gives the tetrapeptide, leucyldiglycylglycine, on hydrolysis and subsequent treatment with ammonia.

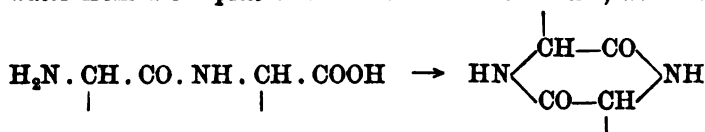


It will be readily understood, from the examples given above, that a large number of polypeptides can be obtained by combining various amino and diamino acids, and a long list of compounds has been prepared in this way. As a class, they show a close resemblance to the natural peptones; the majority are soluble in water; with the exception of some of the di- and tri-peptides they give the biuret reaction; they are precipitated by phosphotungstic acid; they have a bitter peptone-like taste and are readily hydrolysed by acids, and in many cases by trypsin, forming amino acids. The closest resemblance to the natural peptones is found in those polypeptides which have a long chain composed of different amino acid radicals.

The Classification of the Proteins. Many different schemes of classification have been proposed, but owing to our ignorance of the constitution of the proteins, they are all more or less artificial. It is generally believed that the amino acids, which constitute the products of protein hydrolysis, are linked together in the protein molecule, as in the polypeptides, by the union of the amino group of one molecule with the carboxyl group of another. In the case of aliphatic monamino acids the type of grouping may be represented as follows:



Even if it is assumed that this simple type of amino acid condensation is the only one present in the protein molecule, it is clear that the combination of the different types of amino acids, obtained on hydrolysing proteins (p. 398), must give rise to extremely complex systems. There is, however, no reason to suppose that other types of grouping may not be present. E. Fischer suggests the possibility of the presence of piperazine groups in the protein molecule, ring formations of this character being easily accounted for by the elimination of water from a complex of two amino acid molecules, as follows:



It is also possible that the hydroxyl groups in the hydroxy-amino acids are not present in the original protein molecule, but are derived from anhydrides formed by intramolecular condensation.

As previously stated, the extremely limited extent of our knowledge of the molecular structure of the proteins renders a scientific system of classification at present impossible. Nevertheless a system may be devised which is based, not on the properties of the individual proteins, but on their products of hydrolysis. For example, the protamines, a group of basic proteins obtained from fish spermatozoa, commonly yield more than 80 per cent. of diamino acids, and only small quantities of monamino acids, whereas the majority of more complex proteins yield relatively little diamino acids and a large proportion of monamino acids. (An idea of the composition of the products of hydrolysis of some types of proteins may be obtained from the accompanying table (p. 414).) Unfortunately the data concerning the nature and proportion of the various amino acids, derived from different proteins, are insufficient to serve as the sole basis for a system of classification. But there is an additional fact upon which an arrangement may be based. Many complex proteins on gentle hydrolysis are resolved into two portions, one essentially protein and the other non-protein in character. An example of such a substance is furnished by the blood-pigment, *oxyhaemoglobin*, which is readily resolved into a protein substance, *globin*, and an iron-containing non-protein substance, named *haematin*. These complex proteins which contain a non-protein portion are termed *proteides*, whilst the groups in the original molecule which yield the non-protein substance are termed *prosthetic groups*. It is therefore possible to sub-divide some of the proteins into different classes according to the nature of their prosthetic groups.

THE PROTEINS

Name of Protein.	Class of Protein.	Glycocol.	Alanine.	α -Amino- isovaleric acid.	Leucine. { Iso-leucine. }	Aspartic acid.	Glutamic acid.	Serine.	Cysteine.	Lysine.	Arginine.	Proline.	Oxyproline.	Histidine.	Tryptophane.	Phenylalanine.	Tyrosine.
Salmine	Protamine	0	0	4.3	0	0	0	7.8	0	0	87.4	11.0		0	0	0	0
Thymus histone	Histone						3.66			7.7	14.86			1.21			6.81
Edestine (from hemp seeds)	Globulin	3.8	8.6		22.7	4.25	6.3	.83	.25	1.65	14.17	1.7	2.0	2.19	+	2.4	2.13
Haemoglobin	Chromoproteide	0	4.19		30.0	4.43	1.73	.56	.31	4.28	5.42	2.84	1.01	10.96	+	4.24	1.88
Casein	Phosphoprotein	0	+	+	much	+	+	.43	+	5.8	4.8	3.2	.28	2.6	2.0	3.5	4.5
Keratin (from horn)	Unclassified	.34	1.20	5.70	13.80	2.50	3.00	.68	7.0	+	+	3.00				3.00	4.58

The following scheme for the division of the proteins into six main classes must be considered as a convenient rather than a strictly scientific arrangement.

- (1) Protamines.
- (2) Histones.
- (3) Albumins and globulins.
- (4) Proteides (nucleoproteides, chromoproteides, glycoproteides).
- (5) Phosphoproteins.
- (6) Unclassified proteins ('albuminoids').

A special description of the general properties of each of these classes of substances is found in the following pages, together with a few details of some of the more important individual substances.

The Protamines and Histones. The protamines¹ comprise a small number of proteins which have a very limited distribution. They are far simpler in constitution than such proteins as egg-albumin, and their properties show corresponding differences. They occur in combination with nucleic acids (p. 421) in the form of nucleoproteides, which constitute practically the whole of the head or nucleus of the spermatozoa of certain kinds of fish.

These substances were first investigated in 1874 by Miescher, who obtained an impure protamine from salmon testicles, but, although he accurately determined the chief characteristics of the base, these early observations were overlooked. The detailed study of the protamine group is almost entirely due to Kossel and his pupils.

The protamines are found only in the spermatozoa of a few kinds of fish, among which the salmon, herring, sturgeon, mackerel, and carp are the most important. They are prepared by extracting the ripe spermatozoa with dilute sulphuric acid and precipitating the filtered solution with alcohol. In this way a crude protamine sulphate is obtained as a white flocculent precipitate which is only moderately soluble in water. On concentrating a solution of the protamine sulphate, a clear, colourless oil settles out, which contains most of the sulphate. This oil can be separated and the protamine further purified by conversion into the picrate.

The protamines are strongly basic substances which absorb carbon dioxide from the air, and form fairly well-defined, sparingly soluble salts with platinic chloride, cupric hydrate, and silver oxide. Their aqueous solutions are not coagulated by boiling, but precipitates are

¹ A complete account of the protamines together with the whole of the literature will be found in a 'Sammel-Referat', Kossel, in the *Biochemisches Centralblatt*, 1906, v, pp. 1 and 83.

formed by the usual protein precipitants, such as phosphotungstic, chromic and picric acids, and potassium ferrocyanide.

The proportion of nitrogen (25–30 per cent.) in the protamines is higher than in any other class of proteins, but they contain neither phosphorus nor sulphur. With the exception of cycloptertine and cyprinine the protamines do not react with Millon's reagent, and tyrosine is not found among their products of hydrolysis. Cycloptertine gives the Adamkiewicz reaction, but the tryptophane complex is uniformly absent from the other members of the group.

With one exception they all yield remarkably large amounts of arginine on hydrolysis, and this fact no doubt accounts for their strongly basic properties. The following table¹ contains the main results of these investigations.

Hydrolytic Products of the Protamines.

<i>Source of Protamine.</i>	<i>Name of Protamine.</i>	<i>Arginine.</i>	<i>Lysine.</i>	<i>Histidine.</i>	<i>Alanine.</i>	<i>Serine.</i>	<i>Amino- valeric acid.</i>	<i>Proline.</i>	<i>Leucine.</i>
Mackerel	Scombrine	88.8	—	—	6.8	—	—	8.8	—
Salmon	Salmine	87.4	—	—	—	3.2	1.6	4.3	—
Herring	Clupeine	89.0	—	—	+	+	+	+	—
Sturgeon	Sturine	68.4	8.4	11.8	+	—	—	—	+
Carp	Cyprinine	8.6	80.8	—	?	?	+	?	?

It will be seen that among the products of the hydrolysis of salmine, clupeine, and scombrine, about 88–89 per cent. of the total nitrogen is found as arginine, and a further 10 per cent. is present in the form of monoamino acids (alanine, serine, aminovaleric acid and proline), but lysine and histidine are absent.² Thus the products of hydrolysis, which have been identified, represent almost the whole of the original protamine. This is a matter of some interest, because in the case of the more complicated proteins it has so far been impossible to account for more than about 70 per cent., and frequently very much less of the original material.

Salmine, which has been more completely investigated than the other protamines, consists approximately of 10 mols. arginine, 2 mols. serine, 1 mol. α -aminovaleric acid, and 2 mols. proline.

¹ The numbers express the percentage of nitrogen present as amino acids compared with the total nitrogen.

² The details of these methods, which depend essentially upon the varying properties of the silver salts of histidine, arginine, and lysine, will be found in papers by Kossel and his pupils in the *Zeit. physiol. Chem.* (Cf. especially Kossel and Kutscher, 1900, 31, 165.)

These results are in agreement with a formula such as $C_{81}H_{156}N_{45}O_{18}$ with a minimal molecular weight of 2045. Although in the present state of our knowledge this formula can obviously have no claim to exactness, it at least indicates the extreme complexity of even the simpler proteins.

By the regulated action of acids and enzymes, it has been possible to prepare substances intermediate between the protamines and amino acids. These substances have been called *protones*, and the name suggests a relationship to the protamines which may be regarded as similar to that existing between proteins and peptones. The protones give the biuret reaction and resemble the simple polypeptides in most respects; up to the present, however, little progress has been made in the effort to obtain them in a well-defined form.

Faintly alkaline solutions of the protamines yield precipitates with coagulable proteins and certain proteoses which bear the closest resemblance to the naturally occurring *histones*. The latter are substances of great biological significance, and, like the protamines, are found in combination with nucleic acids. The more important histones have been prepared from the nucleated red blood-cells of birds,¹ from certain animal glands, especially the thymus,² and from the spermatozoa of the cod, mackerel, sea-urchin,³ and certain other fish.⁴ It appears that the unripe testicles of all fish contain histones, but in a few cases the process of ripening is accompanied by a conversion into protamine, although generally the histone persists.

The histones are distinctly basic substances with a high percentage of nitrogen (17–20 per cent.). Their properties vary considerably according to the source from which they are derived, and, as a consequence, the group as a whole is not very clearly defined. The histones show resemblances to the protamines on the one hand, and to the coagulable proteins and proteoses on the other. In most cases their solutions are not coagulated on heating, except in the presence of salts, and their basic character is inferred from the fact that most of them are precipitated by ammonia. On hydrolysis, the histones yield a larger proportion of basic products than the typical coagulable proteins, and this is clearly in harmony with the view that they are to be regarded as occupying a position

¹ Kossel, *Zeit. physiol. Chem.*, 1884, 8, 511.

² Lillienfeld, *Zeit. physiol. Chem.*, 1894, 18, 478; Lawrow, *Zeit. physiol. Chem.*, 1899, 28, 888.

³ Matthews, *Zeit. physiol. Chem.*, 1897, 23, 899.

⁴ There are various special ways of obtaining the histones, but one common method is to extract the compound of histone and nucleic acid with water. The histone is liberated from the nucleic acid by means of hydrochloric acid and then precipitated by ammonia.

intermediate between the protamines and the proteins of the egg albumin type. Thus, the histone prepared from the spermata of the codfish (*Gadus*-histone) yields, on hydrolysis, 26.8 per cent of its nitrogen in the form of arginine, although many typical proteins yield less than 10 per cent.

Globin, the main protein constituent of haemoglobin, exhibits many of the properties of the histones and may be considered as belonging to the group. It will be referred to later under haemoglobin (p. 424).

The Albumins and Globulins. Albumins and globulins are coagulable proteins forming the more important constituents of the majority of animal and vegetable tissues. They contain sulphur, little or no phosphorus, and, with the exception of a carbohydrate group, no other prosthetic group. They may be regarded as the most typical proteins. Although a large number of albumins and globulins are known, it will be impossible to do more than indicate their general properties and consider one or two selected substances in slight detail.

Albumins are specially characterized by their solubility in distilled water, and by the fact that they are salted out from solution much less readily than the globulins and most other proteins. Salts, such as magnesium sulphate and sodium chloride, fail to precipitate the albumins, but they are precipitated by complete saturation of their solutions with ammonium sulphate. The most important members of the group are egg-albumin and serum-albumin, both of which have been obtained in the form of well-defined crystals by salting out an acid solution with ammonium sulphate under certain special conditions.¹ It is, however, doubtful if the crystalline compounds so obtained are identical with the products as they occur in nature. More probably a very slight amount of alteration has taken place during crystallization, and the crystals represent a salt formed by the combination of the albumin and the acid used in the process. The chemical difference is apparently so slight that at present it has little practical importance. The products of hydrolysis of serum- and egg-albumin include the majority of amino acids, and consequently all the typical protein tests are given by these albumins. Both, on hydrolysis, yield glucosamine in addition to the other products, and from egg-albumin, it is said that as much as 10-11 per cent. is obtainable.²

¹ Hofmeister, *Zeit. physiol. Chem.*, 1889, 14, 168; F. G. Hopkins, *Journ. of Physiol.*, 1895, 23, 180.

² Langstein, *Zeit. physiol. Chem.*, 1900, 31, 49.

The globulins, which are much more numerous than the albumins, are a very important class of substances. They are found in the blood, in most animal tissues, in eggs, and traces also in milk, and include a large number of vegetable proteins. As far as ultimate composition and products of hydrolysis are concerned, they can scarcely be distinguished from the albumins, but the two classes exhibit very different solubilities. The globulins possess the remarkable property of dissolving in water containing small quantities of inorganic salts, but they are precipitated when the salt concentration falls below a certain level either by dilution or dialysis;¹ they are insoluble in pure water and dilute acids, but readily dissolve in alkaline solution, from which they may be precipitated by weak acids, so that they appear to be feebly acid substances; they are much more readily salted out from solution than the albumins, and, unlike the latter, they are precipitated by saturation with magnesium sulphate or by half-saturation of the solution with ammonium sulphate.

Serum-globulin, which is perhaps the most carefully investigated of the globulins, is prepared by adding an equal volume of saturated ammonium sulphate solution to blood-serum. It is an unstable substance, readily passing over into insoluble modifications which do not dissolve in dilute salt solutions. Serum-globulin is probably a mixture of many different globulins.

The globulins give the typical protein reactions, and their products of hydrolysis include all the common amino acids. Most of the globulins yield, on hydrolysis, a substance of a carbohydrate character, which, in the case of egg-globulin, has been identified as glucosamine.

Reference must be made to thyreoglobulin, the remarkable globulin of the thyroid gland. This substance, which was discovered by Baumann, has all the properties of serum-globulin, but contains a considerable though varying quantity of iodine.² The iodine appears to be contained in a prosthetic group, for on hydrolysis with acids or enzymes an iodine-rich substance (14.2 per cent.) named *iodothyryn* is liberated. Both the globulin and iodothyryn have remarkable pharmacological properties, possessing great curative value in cases of myxoedema and cretinism.

Some of the muscle proteins and a protein circulating in the

¹ A discussion of this and other properties of the globulins from the standpoint of physical chemistry will be found in the Royal Society Croonian Lecture for 1906 by W. B. Hardy, and *Journ. of Physiol.*, 1906, 33, p. 251; also J. Mellanby, *Journ. of Physiol.*, 1906, 33, p. 388.

² Oswald, *Zeit. physiol. Chem.*, 1899, 27, 14; 1901, 32, 121.

blood, named *fibrinogen*, show close analogies to the globulins. They have the common property of clotting at low temperatures and forming two insoluble proteins, *myosin* and *fibrin*. The muscle proteins have been investigated by Halliburton and von Fürth,¹ whilst fibrin, on account of its connection with the phenomenon of blood-clotting, has attracted the attention of a large number of chemists.

Many vegetable albumins and globulins have been carefully studied, and our knowledge of these substances is in some cases more complete than of the animal proteins. The early investigations were made chiefly by Ritthausen,² and have been continued by Osborne³ and others. Some of them occur, or have been obtained, in the crystalline form, and offer promising material for further investigation. Perhaps the most important member of this group is *edestin*, which has been prepared from the seeds of hemp, flax, linseed, cotton, and from other sources. The substances obtained from these various materials are all very similar and closely resemble the animal globulins. Some curious vegetable proteins, which are soluble in dilute alcohol, are found in maize, corn, and other seeds, that from maize being known as *zein*. Many other vegetable proteins have been carefully examined, details of which will be found in special text-books.

The Proteides. The proteides are more complex substances than any of the proteins which have so far been considered. They are resolved by the action of acids or enzymes into two parts; one of these constituents is either a protamine, a histone, or a still more complex protein; the other may have a widely varying nature and is known as the *prosthetic group*.

The proteides may be divided, according to the character of these groups, into three main classes—nucleoproteides, chromoproteides and glucoproteides.

Nucleic acids represent the prosthetic group in the first class of substances; they are characterized by the presence of a large amount of phosphorus and yield, on hydrolysis, many interesting products. The prosthetic group in the chromoproteides is represented by coloured substances, while the glucoproteides contain carbohydrate groups.

¹ Halliburton, *Journ. of Physiol.*, 8, p. 133; von Fürth, *Arch. exper. Path. u. Pharm.*, 1895, 36, 281.

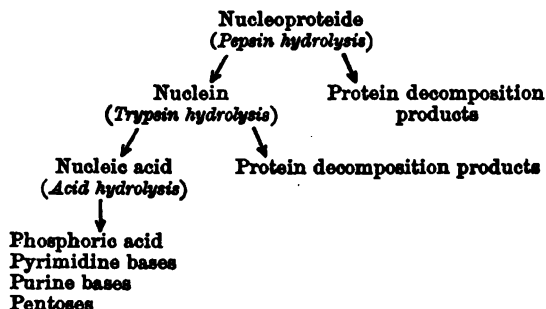
² H. Ritthausen, *Die Eiweisskörper der Getreidearten, Hülsenfrüchte und Oelbamen*, Bonn, 1872.

³ T. B. Osborne. Many papers in *Amer. Chem. Journ.*, *Journ. Amer. Chem. Soc.*, and *Amer. Journ. of Physiol.*, from 1892.

The Nucleoproteides. The simplest nucleoproteides are found in the spermatozoa of fish and have been carefully investigated by Miescher, Schmiedeberg, and especially by Kossel.¹ They may be regarded as salts formed by the union of a basic protein, which is either a protamine (p. 415) or histone (p. 417), with nucleic acids. This compound of protein and nucleic acid may represent as much as 96 per cent. of the dry matter in the head, or nuclear portion, of the spermatozoa. Nucleoproteides of a somewhat different type have been prepared from a very large number of animal tissues, and, of these, the preparations derived from the thymus and pancreas have been most carefully studied. The proteins in these nucleoproteides are usually much less basic than those obtained from spermatozoa. The practical details of the preparation of nucleoproteides from animal tissues leave it doubtful whether they are single individuals, and, as a consequence, the principal interest is transferred to the nature of their prosthetic groups.

When a nucleoproteide is carefully hydrolysed by pepsin, it is found that a portion of the protein is rapidly removed, leaving an insoluble substance, known as *nuclein*, which, however, still contains a certain amount of protein. On further hydrolysis, either with dilute acids or with trypsin, the remaining protein is removed, and nucleic acid and protein decomposition products remain in solution.

The nucleic acids are strongly acid substances which contain a high percentage of phosphorus. On hydrolysis with acids at high temperatures they yield a variety of interesting products, which include phosphoric acid, pyrimidine and purine bases and carbohydrates. The successive stages in the hydrolysis of a nucleoproteide may be represented as follows:—



¹ Miescher, *Archiv exper. Path.*, 1896, 37, 100; Schmiedeberg, *Archiv exper. Path.*, 1900, 43, 57; Kossel, many papers in *Zeit. physiol. Chem.*, and *Ber.* from 1898. A monograph by Burian on the chemistry of Spermatozoa in Ascher and Spiros' *Ergebnisse der Physiologie*, vol. iii, p. 48, 1904, should be consulted.

Among the pyrimidine bases, uracil, thymine, and cytosine have been identified (p. 878).

The purine bases include adenine, guanine, hypoxanthine, and xanthine. The nature of the carbohydrate group is in many cases not definitely known, but usually substances are present which yield the reactions of a pentose, and, in the products from pancreas nucleoproteide, *l*-xylose has been definitely identified.¹

In addition to these substances, Kossel and Neumann² have found that certain nucleic acids yield levulinic acid on hydrolysis, which is usually assumed to be a secondary product derived from the decomposition of a hexose, present in the nucleic acid molecule. It has also been stated that glycerol is present among the products of hydrolysis of the nucleic acid from the pancreas.³

Comparatively little is known of the relative quantities of the various hydrolytic products, but the following analysis of guanylic acid, the nucleic acid of the pancreas, and tritico-nucleic acid⁴ from wheat-meal, may be taken as typical:

1 mol. of guanylic acid yields	{	4 mola. phosphoric acid
		4 mola. guanine
		8 mola. <i>l</i> -xylose
		8 mola. glycerol
1 mol. of tritico-nucleic acid yields	{	4 mola. phosphoric acid
		8 mola. pentose
		2 mola. uracil
		1 mol. adenine
		1 mol. guanine

Small quantities of other products, which have not yet been identified, are formed at the same time.

Extremely little is known of the way in which these products of hydrolysis are grouped together in the nucleic acid molecule, and, although certain structural formulae have been suggested, they have but little value. It is not even certain in what form the phosphorus is present, although its occurrence in the form of a simple phosphate of a pyrimidine or purine base is improbable. Burian⁵ has recently shown that purine derivatives, in which the iminazole ring is intact and in which the hydrogen attached to the nitrogen atom in position 7 is unsubstituted, yield coloured products on treatment with aromatic diazo compounds in alkaline solution. Guanine, for example, reacts with diazobenzene sulphonic acid in the following manner:

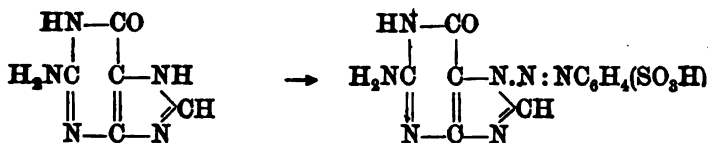
¹ Neuberg, *Ber.*, 1902, 35, 1467.

² *Zeit. physiol. Chem.* 1894, 27, 2215.

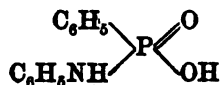
³ Osborne and Harris, *Zeit. physiol. Chem.*, 1902, 36, 85.

⁴ Bang, *Zeit. physiol. Chem.*, 1900, 31, 411.

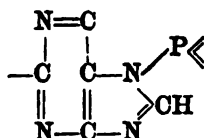
⁵ *Ber.*, 1904, 37, 696, 708.



The nucleic acids themselves do *not* give this reaction, although their products of hydrolysis readily do so. Burian, therefore, concludes that the purine bases are united to the rest of the nucleic acid molecule by the nitrogen atom in position 7. The fact that the nucleic acids are readily hydrolysed by acids, but are very resistant to alkalis, suggests the possibility that the nitrogen atom is directly attached to phosphorus, since the organic phosphorus bases, such as anilino-phenylphosphoric acid,



which possess this structure, show a similar behaviour. It is, therefore, not improbable that the following complex is present in the nucleic acid molecule:



The mode in which the pyrimidine and carbohydrate groups are combined in the nucleic acid molecule is unknown.

Chromoproteides. Very few coloured protein substances are known, and of these, haemoglobin, the red colouring matter present in the blood of vertebrates, is the only one which is widely distributed. Haemocyanine is the main constituent of the blood of the octopus and similar animals, and resembles haemoglobin closely in many respects. It is an interesting fact that both these proteides contain metals in their prosthetic groups. Haemoglobin contains 0.47 per cent. of iron, whilst haemocyanin contains 0.88 per cent. of copper. A few other coloured proteins from lower types of organisms have been described, but they have not been fully investigated and will not be referred to here.¹ The chromogenic group in all coloured proteins is probably contained in the prosthetic group, and not in the protein part of the molecule.

¹ See *Vergleichende chemische Physiologie der niederen Tiere*, by von Fürth: Gustav Fischer, Jena, 1903.

Haemoglobin. Haemoglobin consists of a colourless protein, named *globin*, united to a coloured prosthetic group. Perhaps the most remarkable property that haemoglobin possesses is its ability to enter into combination with certain gases, among which oxygen, carbonic oxide, and nitric oxide are the most important. The product of the combination of haemoglobin and oxygen is known as *oxyhaemoglobin*. It was long ago obtained in the form of well-defined crystals, and has been the subject of numerous investigations. Many methods have been devised for its preparation, so that it can be obtained more readily and in a purer state than is possible with most of the other proteins.¹

Both oxyhaemoglobin and haemoglobin crystallize in many different forms, almost all of which belong to the rhombic system, and are obtained from the blood of various animals, but, on repeated crystallization, the forms interchange, so that it is not certain that the different crystals represent differently constituted substances. Solutions of haemoglobin and its derivatives have been examined spectroscopically by a large number of investigators, and show well-defined absorption bands, details of which will be found in text-books on Physiological Chemistry.

The fact that haemoglobin solutions exert a distinct osmotic pressure has already been mentioned, and the question of its molecular weight, deduced both from osmotic pressure determinations, and from the proportion of iron in the molecule, has also been discussed (p. 898).

A great many elementary analyses of haemoglobin have been made, and the following numbers are selected from closely agreeing analyses of horse haemoglobin by Hoppe-Seyler, and by Nencki:

C = 54.8 ; H = 7.0 ; N = 17.2 ; S = 0.65 ; Fe = 0.47.

On gentle oxidation with potassium ferricyanide, haemoglobin is converted into an interesting substance known as *methaemoglobin*. It has been obtained in crystals, and is isomeric with oxyhaemoglobin, but, unlike the latter substance, the oxygen cannot be removed by a stream of a natural gas. It is found in the urine in disease, and may be identified spectroscopically. On reduction, it is reconverted into haemoglobin.

The Resolution of Oxyhaemoglobin into Globin and Haematin. The protein, globin, is very loosely combined with its prosthetic group, haematin, and the resolution of oxyhaemoglobin is brought about by very weak acids. This decomposition was observed as long ago as

¹ F. N. Schulz, *Zeit. physiol. Chem.*, 1898, 24, 449.

1864 by Stokes and by Hoppe-Seyler. More recent experiments have shown that oxyhaemoglobin may be decomposed by the action of acids, in the presence of alcohol and ether, in such a way that the colouring matter is dissolved by the ether, while the protein remains in the aqueous portion. The haematin is present in very much smaller quantity than the globin, as may be seen from the following approximate numbers¹: globin = 94.1 %; haematin = 4.5 %. It is found that small quantities of ammonia and fatty acids of the acetic series are formed at the same time. The nature of the union between globin and haematin is quite unknown; but it is almost certain that it is not that of a simple salt.

Globin is a curious protein which has been shown by Schulz² to closely resemble the histones (p. 417). It is soluble in acids, but is precipitated by ammonia. It contains a high percentage of nitrogen (16.9 %), and, on hydrolysis, yields a large proportion of bases (histidine = 11 %, arginine = 5.4 %, lysine = 4.3 %). The amount of histidine is larger than that found in the products of hydrolysis of any of the common proteins. The other products of hydrolysis of globin³ are given in the table on page 414.

Haematin and its Derivatives. A large amount of work has been done with the object of determining the nature of haematin; but its exact constitution is still obscure. Although the preparation of haematin in the pure state presents considerable difficulties, a crystalline substance, *haemin*, closely allied to it, is easily obtained. If a drop of blood is warmed on a microscope slide with glacial acetic acid and a trace of common salt, it is found, on cooling, that a quantity of small dark-brown plates and prisms separate out.⁴ These crystals are composed of haemin, and are produced by the action of hydrochloric acid upon haematin, previously liberated from the haemoglobin by the acetic acid. A process for the preparation of large quantities has been devised by Schalféjew⁵ which does not differ in principle from the micro-chemical method. The products obtained by other methods have given slightly varying results upon analysis, but Küster, by the use of a somewhat complicated method of purification, has been able to show that, in all probability, only one haemin exists, and that the substance has the formula $C_{34}H_{44}O_4N_4ClFe$.

¹ Lawrow, *Zeit. physiol. Chem.*, 1898, 26, 848.

² *Zeit. physiol. Chem.*, 1898, 24, 449.

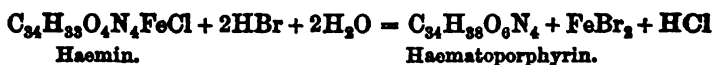
³ Abderhalden, *Zeit. physiol. Chem.*, 1908, 37, 484.

⁴ The formation of haemin crystals constitutes the best chemical test for the detection of blood and is used in conjunction with the spectroscopic method.

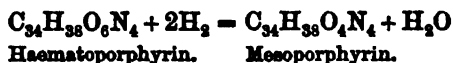
⁵ *Chem. Centralbl.*, 1885, 18, 282.

The relation between haemin and haematin is indicated to some extent by the following observations. Haematin is obtained from haemin by the action of caustic soda, and, according to Küster, has the formula $C_{34}H_{34}N_4FeO_5$. On the other hand, haematin is converted into haemin by the action of hydrochloric acid; consequently, haemin is frequently spoken of as haematin hydrochloride. This, however, is incorrect, as apparently a hydroxyl group is replaced by chlorine. Moreover, if haemin is heated with aniline, hydrochloric acid is removed, a product named *dehydrohaematin* being formed which is not identical with haematin.

Haematin and haemin, as previously mentioned, contain a considerable quantity of iron, but this is readily removed by the action of strong acids, leaving an iron-free pigment named *haematoporphyrin*. The reaction may be represented as follows:



Haematoporphyrin, on partial reduction with hydriodic acid, yields *mesoporphyrin*:



On further reduction with hydriodic acid, the mesoporphyrin is converted into a volatile compound, *haemopyrrole*,¹ to which reference is made below. These substances are of the greatest interest, not only in connection with the structure of haematin, but also with that of bile and urinary pigments and of chlorophyll. Haematoporphyrin is found occasionally in the urine (especially after sulphonal poisoning, which produces considerable blood destruction) and is no doubt derived from haematin, set free from haemoglobin. Mesoporphyrin is probably identical with a substance described under the name of *haematoidin*, which was discovered by Virchow in 1847 in blood extravasations, and also with *bilirubin*, which is one of the best known bile-pigments.

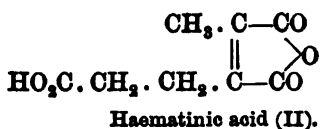
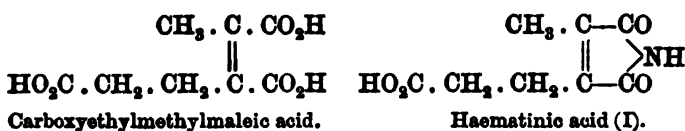
An interesting proof of the chemical relationship existing between chlorophyll and animal pigments has been furnished by Nencki and Marchlewski who showed that a substance, *phyllocyanin*, which, on reduction with hydriodic acid, gave haemopyrrole, could be obtained by the action of acids upon chlorophyll. Moreover, in both chemical

¹ These and other allied investigations by Nencki and his pupils are published in many different journals, but all will be found in Nencki's *Collected Works* (*Gesammelte Arbeiten* von M. Nencki, 2 vols., Vieweg & Sohn, Braunschweig, 1906).

properties and absorption spectra a close similarity exists between many of the degradation products of chlorophyll, obtained by Schunck and Marchlewski, and the decomposition products of haematin. Haemopyrrole readily undergoes oxidation in the air with the production of urobilin, the main pigment of the urine, which may also be produced under certain conditions by the direct reduction of haematin or haematoporphyrin.

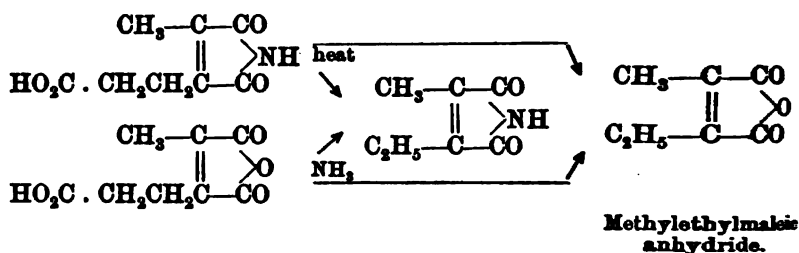
The constitution of haemopyrrole cannot be regarded as definitely settled, and indeed Küster has quite recently brought forward evidence which leads him to the belief that it is not a pure substance. As the oxidation of haematin gives rise to substances which throw considerable light upon the probable structure of haemopyrrole, it will be convenient to discuss the nature of these oxidation products.

Oxidation of Haematin. The investigation of the oxidation products of haematin has been carried out by W. Küster and his pupils.¹ By acting upon haematin dissolved in acetic acid with sodium bichromate, two acids were obtained with the formulae $C_8H_7NO_4$ and $C_8H_5O_6$. Both of these substances were termed *haematinic acids*, and eventually proved to be the anhydride and imide respectively of carboxylethylmethylmaleic acid.

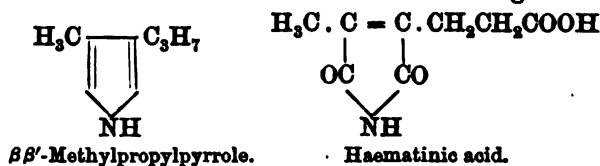


The structure of the haematinic acids follows from the fact that the imide, $C_7H_5O_2N$, obtained by heating haematinic acid (II) with ammonia at high temperatures, is identical with the synthetically prepared imide of methylethylmaleic acid, and the same product is also obtained by the dry distillation of haematinic acid (I). Both the haematinic acids have been converted into methylethylmaleic anhydride which has been repeatedly synthesized. The changes may be represented as follows :

¹ *Annalen*, 1906, 345, 1, and earlier papers.



Nencki and Zaleski considered that the haematinic acids of Küster were derived from the same complex in the haematin molecule as that which yielded haemopyrrole on reduction. From analyses of the picrate, and other salts of haemopyrrole, they assigned the formula $\text{C}_8\text{H}_{13}\text{N}$ to the latter substance, and, mainly from a consideration of the structure of the haematinic acids, they concluded that their substance was probably $\beta\beta$ -methylpropylpyrrole. The relationship between the substances is evident from the following formula :



Various attempts have been made to synthesize $\beta\beta$ -methylpropylpyrrole in order to settle the constitution of haemopyrrole, but so far with doubtful results. Buraczewski and Marchlewski¹ distilled the imide of methylpropylmaleic acid with zinc dust and obtained a minute quantity of a substance which closely resembled haemopyrrole, and which, on oxidation, gave urobilin, but the identity of the substance with haemopyrrole could not be established.

More recently, Küster has given reasons for believing that haemopyrrole is not a single substance. The formula $\text{C}_8\text{H}_{13}\text{N}$, established by Nencki and Zaleski, would harmonize not only with $\beta\beta$ '-methylpropylpyrrole, but also with diethylpyrrole, and with hexahydroisindole. The reduction of haematin is certainly a more complicated reaction than was previously believed, and Küster considers it possible that all the above substances may be formed. Under these circumstances it is impossible at present to profitably discuss the structure of haematin or haemin.

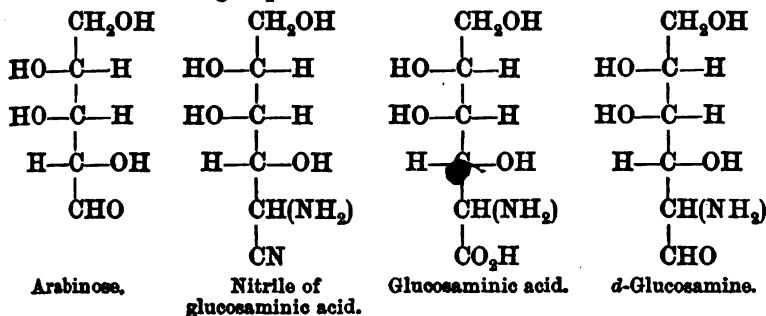
The Glucoproteides. It has long been known that certain proteins yield, on hydrolysis, substances giving the reactions of carbohydrates, but the nature of these substances, which constitute the prosthetic groups of the glucoproteides, was obscure. The study of the carbo-

¹ *Zeit. physiol. Chem.*, 1905, 43, 410.

hydrate groups of the proteins is of great physiological interest, and their investigation was stimulated by Pavy's discovery that certain typical proteins, such as egg-albumin, yield, on hydrolysis, reducing sugars. More recently it has been asserted that carbohydrate groups occur in a variety of proteins, but great caution is necessary in accepting this statement, for it is common to find that as the purification of the protein becomes more thorough, the proportion of carbohydrate obtained on hydrolysis rapidly diminishes. In many cases, however, the presence of a carbohydrate group has been demonstrated, and its nature satisfactorily determined.

The more important of the glucoproteides are known as *mucins* and *mucoids*. The mucins are viscid, tenacious substances which are produced and secreted by the epithelial cells of animals; they also form the chief constituent of the intercellular material of connective tissue. They are readily soluble in dilute alkalis, but are reprecipitated by acetic acid. The mucoids resemble the mucins in most respects, but they are not precipitated from their alkaline solutions by excess of acetic acid. F. Müller succeeded in isolating from mucine a substance, which gave the carbohydrate reactions and identified it as *glucosamine*, while subsequent investigators have shown that it is somewhat widely distributed, and may constitute a large part of the glucoproteide molecule. Mucine of the trachea and mucoids from white of egg and ovarian cysts yield from 80 to 40 per cent. of glucosamine.

Glucosamine has long been known as a constituent of *chitin*, a substance which forms the exo-skeleton of many invertebrates, and its structure has recently been determined by Fischer and Leuchs¹, who were able to synthesize it from arabinose. Arabinose, on treatment with ammonia and hydrocyanic acid, yields the nitrile of glucosaminic acid, and the lactone of this acid, on reduction with sodium-amalgam, gives glucosamine. The relative space arrangement of the amino group is still undetermined.



¹ Ber., 1908, 36, 24.

Glucosamine may be regarded as intermediate between the carbohydrates and the amino acids, and is probably a secondary product derived from the hydrolysis of a more complicated carbohydrate group in the glucoproteide molecule. Thus Leathes¹ was able to isolate from ovarian mucoid a substance which resembles a disaccharose, and which, on hydrolysis, yields glucosamine and a hexose.

It has been asserted that many other prosthetic groups exist in glucoproteides, but further investigation is greatly needed. Schmiedeberg prepared from cartilage mucine a complicated substance containing sulphur which could be converted by hydrolysis successively into a substance named *chondrosin*, and into glucosamine and glycuronic acid; but the recent work of Neuberg and Orgler who failed to isolate glucosamine has thrown considerable doubt on the nature of these substances. On the other hand they obtained a hitherto unknown hydroxyamino acid $C_6H_7(OH)_4NH_2 \cdot CO_2H$, which appears to form a connecting link between the amino acids, glucosamine and the hexoses.

Phosphoproteins. The phosphoproteins, as the name indicates, are proteins which contain a considerable proportion of phosphorus (0.5–1.5 per cent.). In this respect they resemble the nucleoproteides with which they were formerly classified, but they are sharply differentiated from them by the fact that, on hydrolysis, they yield neither purine bases, pyrimidine bases, nor pentoses. The most important members of this group, all of which are closely related, are *casein*, the chief protein constituent of milk, *vitellin*, found in the yolk of eggs, and *ichthulin*, found in the eggs of fishes.

The phosphoproteins are distinctly acid substances, insoluble in water, but readily soluble in alkalis, forming definite salts.² Solutions of these salts do not coagulate on heating, but the protein is readily precipitated by acids. When casein is digested with trypsin, or with 1 per cent. caustic soda, almost the whole of the phosphorus is removed, in the latter case as an inorganic phosphate; but with trypsin, about two-thirds remains in 'organic' combination.³

The phosphoproteins yield all the ordinary protein reactions, and may be readily salted out from solutions by means of ammonium sulphate. The products of hydrolysis of casein have been very carefully studied, and, with the exception of glycocoll, almost all the usual

¹ *Archiv exper. Path.*, 1899, 43, 245.

² The sodium salt of casein is found in commerce under the names 'plasman' and 'nutrose'.

³ Bayliss and Plimmer, *Journ. of Physiol.*, 1906, 33, 489.

amino acids have been isolated. Tyrosine and tryptophane are present in large proportion, and, in addition, Fischer and Abderhalden¹ have isolated an acid named diaminotrioxydodecylic acid, $C_{12}H_{24}N_2O_5$.

Unclassified Protein Substances. A large number of substances closely allied to the typical proteins are known, but cannot be classified under any of the above groups. It has hitherto been customary to name them 'albuminoid' substances, the term indicating their resemblance to the typical proteins. Their exclusion from the main group was due either to their physical properties or to their failure to respond to such tests as the Millon or Adamkiewicz reactions. A further study of both the true proteins and the 'albuminoids' has shown that the distinction between the groups is no longer tenable, for there is no clear line of demarcation, and no chemical tests will serve as a satisfactory basis of separation. Many of these unclassified proteins are insoluble substances, forming important constituents of the skeletal parts of living organisms, but they are not found in animal cells, blood, lymph, or similar fluids. They are all hydrolysed by acids, and many of them also by enzymes, yielding proteoses, peptones, and a variety of amino acids. The proportions of these amino acids vary considerably, which, no doubt, accounts for the physical differences between the members of this group and the typical coagulable proteins. A few of the more important of these substances are mentioned below, but for detailed information special text-books must be consulted.

Gelatin is obtained by the action of steam upon the insoluble protein found in bone and cartilage. On hydrolysis it yields a very large quantity of glycocoll (16 per cent.),² but neither tyrosine nor tryptophane. *Keratin* is the main constituent of hair, hoof, horns, nails, &c. It is a very insoluble substance, and is remarkable for the large amount of sulphur it contains. On hydrolysis it may yield as much as 14 per cent. of cystine.³ A similar substance, known as *neurokeratin*, is found in nerve-fibres. *Elastin* is contained in the yellow elastic fibres of connective tissue and yields on hydrolysis large amounts of leucine, but scarcely more than traces of the diamino acids.⁴ *Fibrosin* and *sericin* are the protein constituents of

¹ This appears to be identical with the caseinic acid of Skraup, *Ber.*, 1904, 37, 1596.

² E. Fischer, Aders, and Levene, *Zeit. physiol. Chem.*, 1902, 35, 70.

³ K. A. H. Mörner, *Zeit. physiol. Chem.*, 1901, 34, 207.

⁴ Kossel and Kutscher, *Zeit. physiol. Chem.*, 1898, 25, 551; Horbaczewski, *Zeit. physiol. Chem.*, 1882, 6, 880.

crude silk. The former, on hydrolysis, yields more than 86 per cent. of glycocoll, 21 per cent. of alanine, and 10 per cent. of tyrosine, but leucine and the diamino acids are present in very small quantity, and glutamic and aspartic acids appear to be completely absent.¹ *Spongia* is an insoluble protein found in sponges, and contains a large proportion of iodine.

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¹ E. Fischer and Skita, *Zeit. physiol. Chem.*, 1901, 33, 171; 1902, 35, 224.

CHAPTER XII

THE BENZENE THEORY

At a time when the paraffins and their derivatives, known as 'the fatty compounds', formed a well ordered and compact group of closely related substances, there remained an unclassified collection of vegetable products, such as balsams, resins, essential oils, and their derivatives, which, from their pleasant perfume, received the name of 'aromatic compounds'.

A closer study of these aromatic compounds revealed a connection between certain members similar to that which had long been recognized among the derivatives of the paraffins. Thus toluene, C_7H_8 , obtained by distilling tolu balsam, bore the same relation to oil of bitter almonds and benzoic acid as ethane to acetaldehyde and acetic acid.

C_7H_8	C_7H_6O	$C_7H_6O_2$
Toluene.	Oil of bitter almonds.	Benzoic acid.
C_2H_6	C_2H_4O	$C_2H_4O_2$
Ethane.	Acetaldehyde.	Acetic acid.

Cymene, $C_{10}H_{14}$, cuminol, $C_{10}H_{12}O$ (from Roman cumin oil), and cumic acid, $C_{10}H_{12}O_2$, prepared by oxidation of cuminol, showed a similar relationship. The first of each series was a stable hydrocarbon, the second exhibited the properties of an aldehyde, and the third was an acid.

But notwithstanding the parallelism which appeared among members of the aliphatic and aromatic groups, a sharp line divided them; indeed, many years elapsed before any direct synthesis of a member of the one group from that of the other served to establish a link between them.

Among the members of the aromatic group there existed a certain family resemblance which was easy to recognize. They contained a higher proportion of carbon than the fatty compounds, and on being broken up into simpler substances, it was found that the products, such as benzene, C_6H_6 , phenol, C_6H_5O , picric acid,

$C_6H_5N_2O_7$, &c., contained 6 atoms of carbon. Any attempt to pass beyond this point and to form substances with 5 or fewer carbon atoms, generally resulted in the complete disintegration of the molecule.

Kekulé's Benzene Formula. Kekulé was the first to draw attention to these facts in his 'Chemie der Benzolderivate', published in 1867, and based upon them a theory which shed a new light on this obscure corner of chemistry. The rapid development of the aromatic group of compounds, which has now become the predominant partner in the two great divisions of organic chemistry, must be attributed in a great measure to this theory which Kekulé expounded in the following words:

'In order to determine the atomic constitution of the aromatic compounds the following facts must be considered:

'1. All aromatic compounds, even the simplest, are comparatively richer in carbon than the corresponding class of fatty compounds.

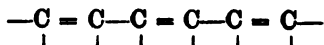
'2. Among the aromatic substances, as among fatty compounds, numerous homologous compounds exist.

'3. The simplest aromatic substances contain at least 6 atoms of carbon.

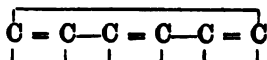
'4. All decomposition products of aromatic substances show a certain family resemblance; they belong to the group of aromatic substances. In more vigorous reactions a part of the carbon in the form of compounds of the fatty group is eliminated, but the main product is always aromatic and contains at least 6 atoms of carbon (benzene, quinine, chloranil, phenol, oxyphenic acid, picric acid, &c.). The decomposition stops with the formation of these products, unless complete destruction of the organic group ensues. These facts, which have been recognized as of general application, justify the supposition that in all aromatic compounds there is one and the same atomic group or common nucleus, which consists of 6 atoms of carbon. Within this nucleus the carbon atoms are in a certain closer connection or denser combination, from which it follows that all aromatic compounds are comparatively rich in carbon. More carbon atoms can then be added to this nucleus in the same manner and according to the same laws which govern the fatty compounds. In this way the existence of homologous compounds may be explained.'

Kekulé then proceeds to show how these 6 atoms of carbon may be so united as to leave 6 single combining units free. In conformity with his view of the constant valency of carbon, Kekulé

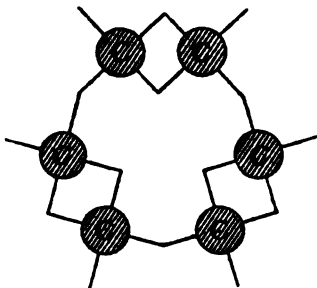
supposes that every alternate linkage is a double one. Six carbon atoms thus arranged in an open chain will have 8 free combining units,



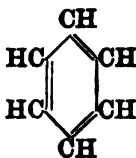
but if the two end carbon atoms are linked together, a closed chain of carbon atoms results with 6 free combining units,



which he represented by the following graphic formula :



If each of the free linkages is attached to a hydrogen atom, the formula for benzene is obtained, and is usually represented in the following manner :



Kekulé's formula for Benzene.

This formula therefore postulates three ethylene linkages. Evidence in favour of such an unsaturated closed chain is afforded by the existence of additive compounds of benzene with 2, 4, or 6 atoms of hydrogen, chlorine, or bromine, but no more. The isomeric hydrocarbon, *dipropargyl*, which is obtained from diallyl tetrabromide by removing hydrogen bromide with potassium hydroxide,



Diallyl tetrabromide.



Dipropargyl.

is undoubtedly an open-chain compound, since it requires 8 additional

atoms of the above three elements for saturation. Moreover, dipropargyl is very sensitive to oxidising agents, whereas benzene is marked by great stability, an indication in itself of some fundamental difference in structure.

Non-Olefinic Character of Benzene. But, on the other hand, the affinity displayed by the olefinic hydrocarbons for the halogens is not exhibited to an equal degree by benzene and its homologues. The halogens form additive compounds with benzene only in presence of sunlight, and the hydrogen halides do not combine at all. There is consequently no strict analogy between the two classes of olefinic compounds. The difference is further emphasized by the action of oxidising agents upon benzene and its homologues. Benzene itself is highly resistant, but if a side-chain is present it is attacked and converted into carboxyl, whilst the benzene nucleus is untouched. Thus methyl and ethyl benzene form benzoic acid on oxidation. The very opposite result might have been anticipated from the well-known behaviour of olefinic compounds, which, on oxidation, break down at the double link. Indeed, so commonly does this occur that the rapid reduction of an alkaline solution of permanganate in the cold was used by Baeyer¹ to ascertain the presence of an ethylene linkage in unsaturated acids.

General Properties of Aromatic Compounds. We have now to consider the action of reagents in forming substitution products, and to compare those products with similar compounds of the aliphatic series. By the term 'aromatic' is usually denoted not only benzene and its derivatives, but other closed-chain compounds, such as naphthalene, anthracene, pyridine, thiophene, &c., which show the general behaviour of benzene. The terms *bensenoid* and *cyclic* are synonymous with aromatic.

An important characteristic of the aromatic compounds is the acidic nature of the nucleus. This is observed in the phenols, which correspond to tertiary alcohols in constitution, yet behave like weak acids, and dissolve readily in caustic alkalis; in the amines, which like aniline are weak bases whose salts redden litmus, or like triphenylamine, which forms no salts at all; in substances such as benzyl cyanide and desoxybenzoin, which contain a replaceable hydrogen in the methylene group, thus resembling the 1:3-diketones,

$C_6H_5 \cdot CH_2 \cdot CN$
Benzyl cyanide.

$C_6H_5 \cdot CO \cdot CH_2 \cdot C_6H_5$
Desoxybenzoin.

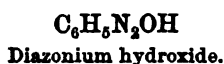
$R \cdot CO \cdot CH_2 \cdot CO \cdot R$
1:3-Diketone.

¹ *Annalen*, 1888, 245, 146.

and like the 1 : 8-diketones undergo condensation by Knoevenagel's method (p. 285). Characteristic, too, is the stability of the simple halogen derivatives of the aromatic hydrocarbons which are unchanged by caustic alkalis, and in fact by most reagents, excepting the alkali metals. By heaping up nitro groups in the nucleus, the acid character may be so far intensified that the halogen, like that in an acid chloride, can be removed by potassium hydroxide, giving a phenol, or by ammonia, forming an amino compound.

The formation of nitro compounds by the action of nitric acid, of sulphonic acids by the action of strong sulphuric acid, and the Friedel-Crafts reaction, have no exact parallel among the aliphatic compounds. To obtain the nitro derivatives of normal paraffins with nitric acid, dilute nitric acid at a high temperature must be employed,¹ although the iso-paraffins are readily attacked by the fuming acid,² and, for preparing the alkyl sulphonic acids, fuming sulphuric acid or the anhydride is necessary.³

We also find among the aromatic compounds diazo and azo compounds, which have only a very limited number of representatives in the aliphatic series. Here again the acidic character—carboxyl in the aliphatic and phenyl in the aromatic series—of the associated group seems to play a part in determining the formation of the compounds in question.



Position Isomerism. Whether or not Kekulé's benzene formula accounts for the distinctive characters of the aromatic compounds, is a question which will be discussed later; but the formula served another purpose. It was designed to explain the special kind of isomerism which is met with among these compounds and usually described as *position isomerism*.

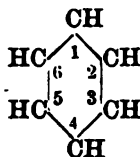
The symmetrical distribution of the hydrogen atoms admits of only one mono-substitution product, and only one such product is known; among the di-derivatives of benzene it soon appeared that

¹ Konowaloff, *Ber.*, 1892, 25 R, 108.

² Francis and Young, *Trans. Chem. Soc.*, 1896, 73, 928.

³ As Marckwald points out, it is scarcely admissible to draw a comparison between benzene and the saturated aliphatic hydrocarbons. Analogies should be sought among the olefinic compounds of the series. Thus the hydroxymethylene compounds (p. 288) which contain the group $-\text{CH}(\text{OH})$ have stronger acid properties than phenol, and halogen compounds of the type $\text{CH}:\text{CHCl}$ contain a more stable halogen than the alkyl chlorides. Also, a substance like cinnamic acid forms with nitric acid a dinitro compound $\text{NO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{CH}:\text{C}(\text{NO}_2) \cdot \text{COOH}$ in which one nitro group replaces hydrogen in the olefinic side-chain and corresponds to nitrobenzene.

many existed in three isomeric forms. If we denote the positions of the carbon atoms in Kekulé's benzene formula (omitting from it the double linkages) by the numbers 1-6,



it is obvious that two elements or groups replacing the hydrogen atoms 1 and 2 will produce a different compound from that formed by replacing those at 1 and 3 and at 1 and 4. As the six carbon and six hydrogen atoms are symmetrically disposed, the substitution of the hydrogen atoms at 1 and 5 will be equivalent to that at 1 and 2, and that at 1 and 6 to 1 and 2, so that three and not more than three di-derivatives are possible. This was in strict agreement with the facts, although the direct proof of the symmetry of the molecule was not forthcoming until later.

Orientation. The necessity for assigning definite positions to the substituents in the different series of isomeric compounds was soon recognized, but it was only after repeated failures that trustworthy methods were at length evolved. The history of the development of the process, which is usually known as *orientation*, presents many features of interest, but cannot be fully discussed here.¹ The first attempts were based on pure assumptions, which being as often wrong as right, led to frequent confusion. Baeyer's view, that mesitylene being formed from acetone must therefore be symmetrical trimethyl benzene, has stood the test of time.

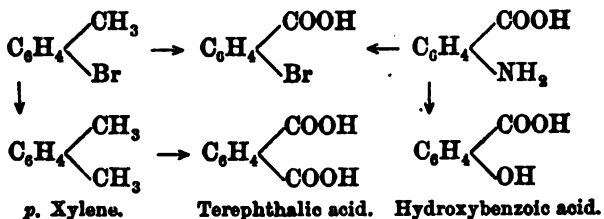
The proof of the symmetrical structure of mesitylene was supplied by Ladenburg in 1874.² He prepared dinitromesitylene which gave nitromesidine by the reduction of one of the nitro groups. The nitromesidine yielded, on nitration of its acetyl derivative, a dinitromesidine, from which, by elimination of the amino group, a dinitromesitylene was obtained, identical with the first. The positions occupied by the two pairs of nitro groups are therefore equivalent. If now the above nitromesidine is converted into nitromesitylene and the latter into mesidine and its acetyl derivative then nitrated, a nitromesidine is formed which is identical with the original nitromesidine. As the interchange of nitro and amino groups gives the

¹ An excellent account is given in Roscoe and Schorlemmer's *Treatise*, vol. iii. part iii (Introduction), and also in the introduction by Richard Meyer to Erlenmeyer's *Lehrbuch der organischen Chemie*, vol. ii (Leipzig, 1882).

² *Ber.*, 1874, 7, 1183; *Annalen*, 1875, 179, 163.

same compound, these two positions must be equivalent, and therefore the three hydrogen atoms, and consequently the three methyl groups, are symmetrically arranged. As mesitylene can be converted into one of the xylenes and into isophthalic acid, the structure of the two latter as meta-derivatives follows. In 1870 V. Meyer converted sulphobenzoic acid, on the one hand, into hydroxybenzoic acid by fusion with potassium hydroxide, and on the other into isophthalic acid by fusion with sodium formate, and thus established these two as meta-derivatives. Salicylic and phthalic acids, since they yielded anhydrides, were assumed to be ortho compounds, and consequently the third hydroxy- and dibasic acid (terephthalic) were para compounds.

The proof of the structure of the two last compounds was furnished by Ladenburg in 1869.¹ Hübner and Petermann² had observed that ordinary bromobenzoic acid, which is related to *m*-hydroxybenzoic acid, gives, on nitration, two isomeric nitrobromobenzoic acids. The latter, on reduction, yield the same aminobenzoic acid, i.e. anthranilic acid, which is related to salicylic acid. As both bromonitrobenzoic acids are derived from the same bromobenzoic acid, the bromine atom in both compounds must have the same relative position to the carboxyl group. The difference must therefore be due to the position of the nitro groups in the two compounds. But since both bromonitrobenzoic acids give the same aminobenzoic acid on reduction, the two nitro groups must also occupy the same relative position to the carboxyl group. This can only happen if the bromine atom or nitro group is not in the para position (see p. 444). Consequently, the third hydroxybenzoic acid, which is related to the third bromo- and amino-benzoic acid, must be a para compound, and as this acid and terephthalic acid are both related to the same bromotoluene, the constitution of terephthalic acid is also given.



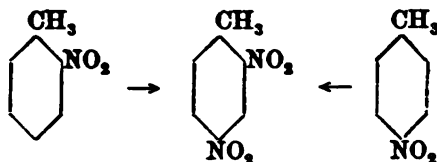
Two out of the three nitrotoluenes were brought into relation with the meta- and para-hydroxybenzoic acids by successively

¹ *Ber.*, 1869, 2, 140.

² *Annalen*, 1869, 149, 129.

oxidising, reducing, and diazotising each of the compounds; the third was consequently the ortho compound.

Petersen¹ pointed out that since ortho- and para-nitrotoluene give the same dinitrotoluene on nitration, the product must contain the two nitro groups in the meta position one to another,



and concluded that dinitrobenzene must also be a meta compound, a deduction which has since proved correct. As *m*-dinitrobenzene is related to a series of simple di-substituted benzene derivatives the structure of these is determined, whilst those of the ortho- and para-compounds are known by their relation to the corresponding dibromobenzenes.

Körner's Absolute Method. The constitution of phthalic acid as an ortho compound was based upon two hypotheses—its relation to the formula for naphthalene and the structure of its anhydride; the formula for isophthalic acid was derived from its relation to mesitylene, the constitution of which was at the time purely hypothetical.

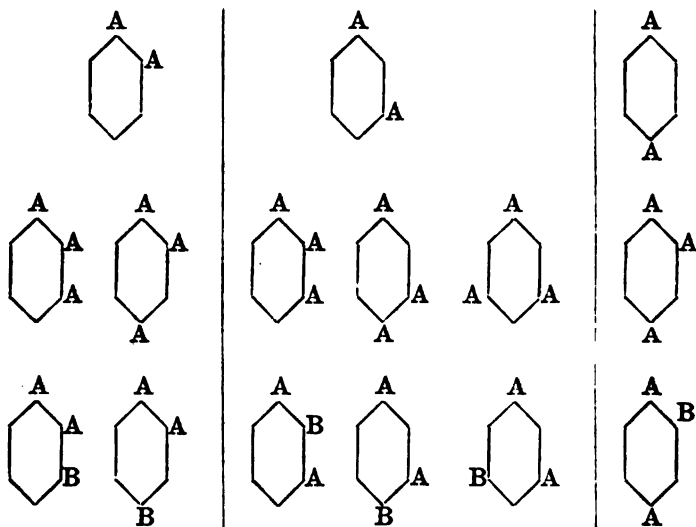
In an important paper published in 1874, 'On the Isomerism of Aromatic Compounds with six Carbon Atoms,' Körner² subjected the methods of orientation, then employed, to a very searching criticism. He pointed out that the structure of the three phthalic acids was too problematical, and their connection with the derivatives of benzene, prepared by direct substitution, too uncertain to serve as a basis of orientation. He held that since it was always open to question whether a reaction, which determined the relation between one compound and another, proceeded in a normal fashion, any method of orientation, to be entirely satisfactory, should be as far as possible independent of the course of chemical change.

Körner's method was based on a principle which assumed the equivalence of the six hydrogen atoms of benzene. A di-derivative of benzene containing similar groups, A A, in the ortho position, can only produce two tri-derivatives by the introduction of a third group.

¹ *Ber.*, 1873, 6, 368; 1874, 7, 58.

² *Gazz. chim. ital.*, 1874, 305; *Jahresb.*, 1875, 299.

A or B. In the same way a meta compound can only produce three tri-derivatives and a para compound only one.



It will be seen from the above scheme that when the three groups in the tri-derivatives are the same, only three isomers are produced in all, whereas if the third group, B, is different from the other two, all the six tri-derivatives are isomeric. Körner applied the principle to determine the constitution of the di- and tri-bromobenzenes. Solid dibromobenzene (m. p. 89°) yields only one nitrodibromobenzene, the isomeric liquid modification is able to form two, and the third, three nitro derivatives. In the same way Körner obtained two tri-bromobenzenes from the first dibromobenzene, one from the second, and three from the third. The first compound is therefore para, the second, ortho, and the third, meta. In practice the method is difficult to carry out, as the complete series of derivatives is not always formed. The reverse process may sometimes be adopted with advantage. If the same di-derivative is obtained from two tri-derivatives, the product is an ortho compound; if from three tri-derivatives, it is meta; if from one only, it is para.

The constitution of the phenylene-diamines, $C_6H_4(NH_2)_2$, has been established by Griess¹ in this way. The six diaminobenzoic acids, all of which are known, yield, on distillation with lime, three phenylenediamines. Three of them give the same phenylenediamine (m. p. 68°) which is consequently a meta compound, two yield a

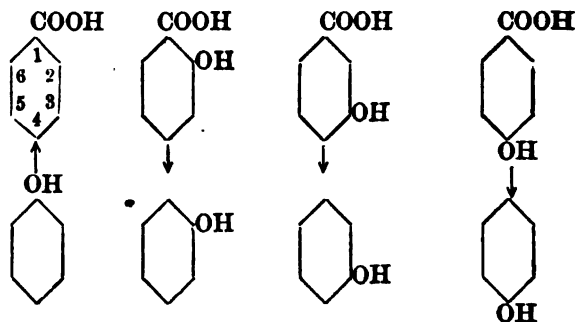
¹ Ber., 1874, 7, 1226.

phenylenediamine (m. p. 99°) which is therefore the ortho compound, and the sixth diamino-benzoic acid forms a phenylenediamine (m. p. 140°) which must be the para compound.

Symmetrical Structure of Benzene. It has already been stated that Kekulé based his formula for benzene upon the general character of the aromatic compounds and upon the symmetrical distribution of the carbon and hydrogen atoms, indirect evidence of which was furnished by the existence of only one mono- and three di-derivatives. The direct proof of the symmetry of the molecule was supplied by the combined researches of Ladenburg, Wroblewsky and Hübner, and Petermann. Ladenburg¹ showed that phenol may be converted by the action of phosphorus bromide into monobromobenzene, which in turn may be transformed, by the action of carbon dioxide and sodium, into the sodium salt of benzoic acid by Kekulé's method (p. 246).



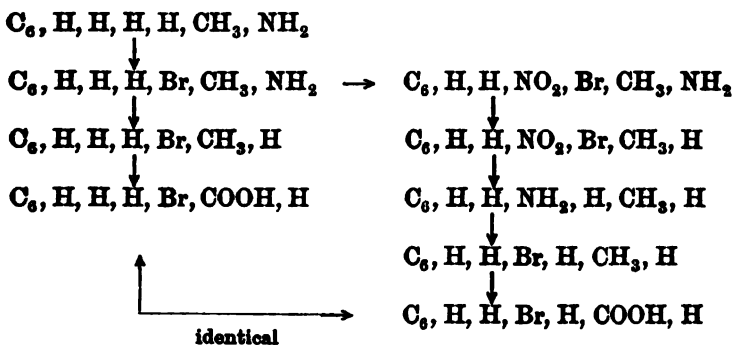
The carboxyl in benzoic acid may be assumed to occupy the same position as the hydroxyl in phenol. Now there are three hydroxybenzoic acids, which may be converted, on the one hand, into benzoic acid and, on the other, into phenol. The benzoic acid and phenol, thus obtained, are identical in every case. If we suppose position 1 to be occupied by carboxyl in the three hydroxybenzoic acids, the hydroxyls will assume positions 2, 3, and 4 respectively, and as the three phenols obtained by removal of carboxyl are identical, and the same as that from which benzoic acid in the first instance was derived, it follows that the positions 1, 2, 3, and 4 are symmetrical or equivalent.



¹ *Theorie der aromatischen Verbindungen*, by A. Ladenburg. Vieweg, Brunswick, 1876.

The same reasoning can be applied to the reduction of the three hydroxybenzoic acids to benzoic acid. The proof of the equivalence of the positions 5 and 6 lies in the fact that there are two pairs of positions which are symmetrically situated with regard to a third pair. It has been shown, for example, that a bromine atom may be introduced into benzoic acid in two different positions relatively to the carboxyl, and yield the same bromobenzoic acid, and, in the same way, a nitro group may replace hydrogen in two other positions and form the same nitrobenzoic acid.

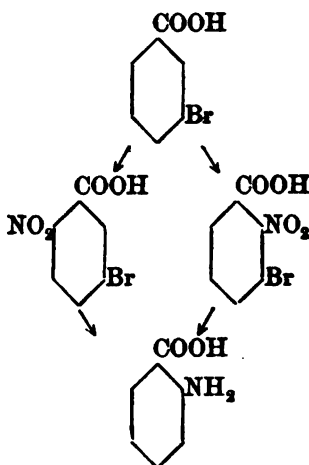
Starting from *p*-toluidine, Wroblewsky¹ prepared a bromotoluidine, and from this, in successive stages, bromotoluene and bromobenzoic acid. He then converted the above bromotoluidine into a nitro-compound, a nitrobromotoluene, a toluidine, and, finally, a bromotoluene and bromobenzoic acid, which were identical with the first two. If direct replacement occurs in the various reactions, it necessarily follows that the first bromine occupies a different position from the second. This will be manifest from the following scheme in which the substituents are given arbitrary positions.



The existence of a second pair of symmetrical positions follows from the observations of Hübner and Petermann,² to which reference has already been made (p. 439). The bromobenzoic acid of Wroblewsky yields, on nitration, two isomeric nitrobromobenzoic acids, which, on reduction, form the same aminobenzoic acid (anthranilic acid).

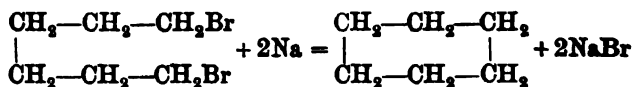
¹ *Ber.*, 1872, 5, 30; *Annalen*, 1873, 168, 153; 1878, 192, 196.

² *Annalen*, 1869, 149, 131.



The two nitro groups, therefore, occupy a second pair of symmetrical positions in regard to the carboxyl. The six carbon and hydrogen atoms are therefore symmetrically grouped, and benzene is, as a whole, a symmetrical structure.

Ring Structure of Benzene. Direct evidence of the ring structure of benzene and its derivatives is afforded by the synthesis of hexahydrobenzene or cyclohexane, and certain of its derivatives from open-chain compounds, and by their identity with the products obtained by the direct reduction of benzene. Thus, Perkin¹ obtained cyclohexane by the action of sodium on hexylene dibromide (p. 247), which is identical with hexahydrobenzene prepared from benzene by reduction.²



Also the *cis*- and *trans*-hexahydro-isophthalic acid and hexahydro-terephthalic acid obtained by Baeyer by the reduction of *iso*- and terephthalic acid (p. 448) are identical with the synthetic compounds obtained by Perkin from disodium pentanetetra-carboxylic ester and methylene iodide in the one case,³ and from disodium butanetetra-carboxylic ester and ethylene bromide in the other⁴ (see p. 250).

The symmetrical ring structure of benzene being thus satisfactorily established, the problem narrows itself down to ascertaining the fate

¹ *Ber.*, 1894, 27, 216.

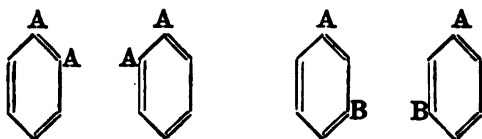
² Sabatier and Senderens, *Compt. rend.*, 1901, 132, 1264.

³ *Trans. Chem. Soc.*, 1892, 61, 172.

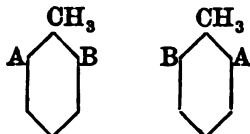
⁴ *Trans. Chem. Soc.*, 1891, 59, 798.

of the fourth carbon bond. Much ingenuity has been displayed in devising formulae, both statical and dynamical, which should solve this problem.

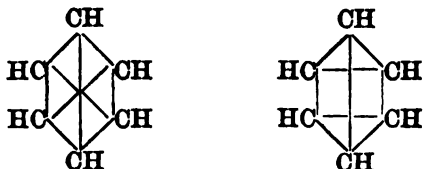
Statistical Formulae for Benzene. Ladenburg employed the proof of the symmetry of benzene to attack a vulnerable point in Kekulé's formula, which represents the carbon atoms as linked alternately by single and double bonds. On this assumption it necessarily follows that in the di-derivatives two different ortho compounds 1, 2 and 1, 6 should exist, and, if the groups are different, two meta compounds also become possible.



No such differences have been observed. Noelting prepared a series of di-halogen derivatives from 2·6 dinitrotoluene, in which, in place of the nitro groups, two different halogens (A, B) were introduced in the inverse order, but he failed to detect any difference in the properties of the compounds.



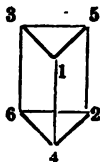
To avoid the difficulty introduced by the double bonds, Claus proposed two formulae, which represent each carbon atom of the ring attached to three others, that is, to two in the ortho and one in the para position, or to two in the ortho and one in the meta position.



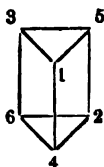
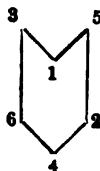
Claus¹ gave the preference to the first or *diagonal formula*, which appeared to suggest a reason for the simultaneous formation of ortho and para compounds, so often observed in reactions with benzene.

¹ *Theoretische Betrachtungen und deren Anwendungen zur Systematik der organischen Chemie*, Freiburg, 1867, p. 207.

Ladenburg's Prism Formula. Ladenburg¹ adopted the second or prism formula. The six carbon atoms are placed at the corners of a regular prism, the edges of which denote the linkages.



The numbered positions correspond to the arrangement of the carbons in the hexagon, as determined by Körner's principle of orientation. The diagonal corners of the prism faces are ortho, those occupying the ends of the vertical edges are para, and those at the corners of the triangular faces are meta positions. Kekulé objected to Ladenburg's formula on the ground that it did not admit of the formation of additive compounds in a satisfactory manner. To convert benzene into cyclohexane it was necessary to have recourse to the doubtful expedient of breaking one para and two meta linkages:

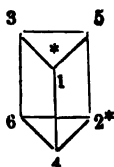
Benzene, C_6H_6 .Cyclohexane, C_6H_{12} .

Moreover, the introduction of two different groups into the prism formula gives rise to molecular asymmetry, which implies the existence of optical enantiomorphs. All attempts to resolve such compounds have been fruitless (p. 95), and, what is even more significant, there is no single instance of an optically active compound of benzene, among the many derivatives found in nature, which owes its activity to the asymmetry of the nucleus. But the most complete refutation of Ladenburg's formula has been furnished by Baeyer. He showed that, of the three hexahydrophthalic acids, it is only the ortho compound which readily forms an anhydride, for the meta compound must be heated with acetyl chloride to give it, and the para compound under no conditions exhibits this change.

According to Ladenburg's formula, phthalic acid on reduction

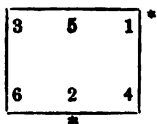
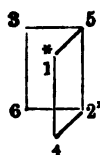
¹ *Ber.*, 1869, 2, 141, 272.

should produce a meta or a para cyclohexane derivative, depending upon which sets of bonds are removed. The process may be graphically represented in such a way that, after the three links are removed, the two prism faces are folded back like the covers of a half-open book.

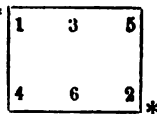
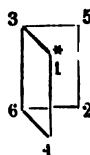


* = COOH

Phthalic Acid.



Meta

**Para.**

Hexahydrophthalic acid according to the prism formula.

It is difficult to reconcile these formulae with the existence of an anhydride, which is more stable than that produced by carboxyls in the ortho position, as denoted by Kekulé's formula.

In reply to Ladenburg's criticism of Kekulé's formula, V. Meyer¹ pointed out that the difference in the two ortho positions was not produced by any alteration in the relative positions of the atoms, as, for example, in the α - and β -derivatives of acrylic acid or propylene, but only by the more delicate distinction of single and double bonds, the exact significance of which is unknown.

Kekulé's Dynamic Hypothesis. Kekulé¹ took a similar view of the question. In order to account for the existence of only one ortho derivative, he brought forward his dynamic hypothesis. Valency, he suggested, may have a mechanical meaning, representing the number of contacts with other atoms experienced by an oscillating atom in unit of time. Two atoms of quadrivalent carbon, linked by one combining unit of each, will perform four complete oscillations, striking each other and also three other atoms in the unit of time, during which period the univalent atom of hydrogen will make a single oscillation. A doubly linked carbon atom will come in contact twice with its neighbouring carbon atom in the same period and also strike two other atoms.

¹ *Annalen*, 1870, 156, 265; 1871, 159, 24.

² *Annalen*, 1872, 162, 85.



Applying this hypothesis to the benzene formula, carbon 1 will strike carbon 2 twice, hydrogen once, and carbon 6 once in the following order :

2, 6, H, 2.

In the second period the order will become :

6, 2, H, 6,

in which carbon 6 is struck twice and carbon 2 once, to be followed in the third period by a recurrence of the first order and so forth. This will naturally take place with all the atoms of the ring. Kekulé supposes that if the first of the above formulae for benzene represents the contacts made during the first unit of time, constituting the first phase, the second formula will depict the second phase, and, as these phases are constantly alternating, there will be an equal number of molecules at any one moment in both phases. The difference between the two ortho positions is, therefore, more apparent than real. But this hypothesis would imply a more rapid motion of the carbon than of the hydrogen atom, which is opposed to the kinetic theory.¹ On the other hand, the observations which have been discussed under tautomerism (p. 202) make it conceivable that some such oscillatory motion of atoms or groups may occur.²

Baeyer's Researches on the Constitution of Benzene. In his classical research 'On the Constitution of Benzene', Baeyer³ sought to decide between the two formulae of Claus and Kekulé, which had alone survived, by an exhaustive inquiry into the reduction products of the phthalic acids. Although this investigation has greatly extended our knowledge of the hydrocyclic compounds, and exhibited their striking analogy with the aliphatic compounds, it cannot be said that the main problem has approached much nearer to its solution.

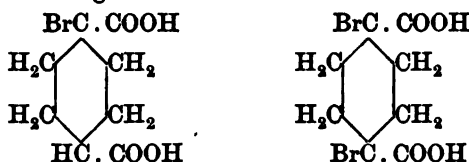
Baeyer himself has frankly admitted as much. 'The task,' he says, 'which I set before me on commencing these researches was to elucidate the constitution of benzene, and not to seek an experimental verification of any particular hypothesis. As a consequence of this resolution I have more than once changed my views, according as

¹ Michaelis, *Ber.*, 1872, 5, 468.

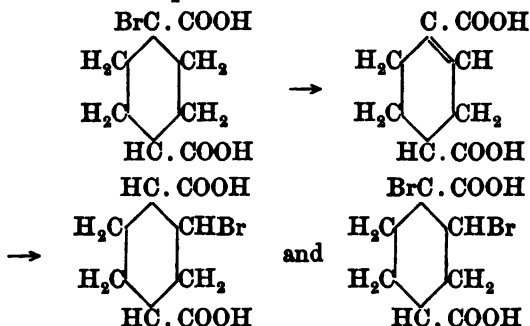
² In this connection Knoevenagel's theory of the atomic motion of unsaturated carbon atoms may be mentioned, *Ber.*, 1903, 36, 2303. In the case of benzene each of the carbon atoms is supposed to rotate in opposite directions to its neighbours, thus alternately making and breaking the double link.

³ *Annalen*, 1887, 248, 108; 1889, 251, 257; 1890, 256, 1; 258, 1, 145; 1892, 266, 169; 269, 169.

the sum of experimental evidence appeared to favour one or another theory. And I would ask the reader not to be astonished because I now give prominence to a hypothesis which I have previously combated, nor to hold me inconsistent if I should chance in the course of time to transfer my allegiance to another theory. . . . No conclusion can be drawn as to the structure of benzene derivatives from their behaviour on reduction.¹ Baeyer's attention was first directed to the diagonal formula of Claus, with the object of ascertaining whether diagonal or *para* linkages exist, and as a preliminary step he began by studying the conditions under which they might conceivably be formed. Terephthalic acid yields, on reduction, hexahydroterephthalic acid, and the latter, on treatment with bromine, is converted into a mono- and a di-bromo compound having the following constitution :

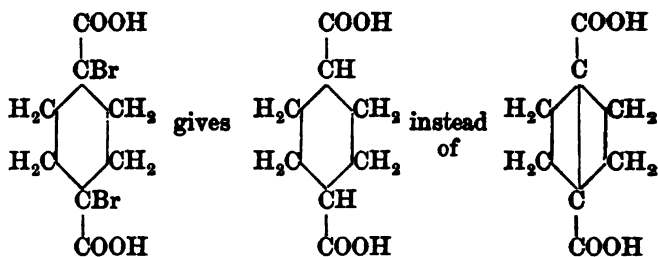


By analogy with the general behaviour of acids on bromination the bromine attaches itself to the α -carbon. The experimental verification of the above structure of the bromine derivatives is as follows: by the action of alcoholic potash on the monobromo compound hydrogen bromide is removed, and a tetrahydroterephthalic acid is formed which reunites with hydrogen bromide to give a different monobromo derivative from the original, and also with bromine to form a dibromo compound which is isomeric with that obtained by direct bromination. These changes can only be satisfactorily explained on the above assumption, namely, that the bromine enters the α -position.

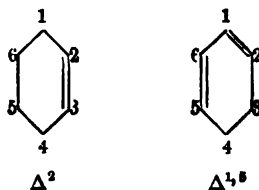


¹ *Annalen*, 1892, 269, 176; see also *Year-Book of Science*, 1898, 225.

The two dibromo compounds show a remarkable difference in their behaviour with zinc dust and acetic acid. Whereas the bromine is readily removed from the compound which contains the bromine atoms in the ortho position, re-forming tetrahydroterephthalic acid with a double link between the two ortho carbons, the effect on the bromine atoms in the para position is to replace them by hydrogen and form the original hexahydro acid. No para linkage is therefore produced where, according to Claus's formula, it would be most natural to expect its appearance.



The diagonal formula was accordingly rejected, only to be reinstated later in a modified form. The change of view was the result of observations made by Baeyer in extending his experiments on the reduction products of the phthalic acids, which will now be briefly described. It should first be stated that the large number of products obtained by the reduction of phthalic,¹ isophthalic,² and terephthalic³ acids has necessitated a special system of notation. The carbon atoms of the nucleus being numbered from 1 to 6 in the order of the figures on a clock face, the position of the double bond is indicated by the Greek Δ followed by the number of the initial carbon of the double linkage, as in the following two examples.



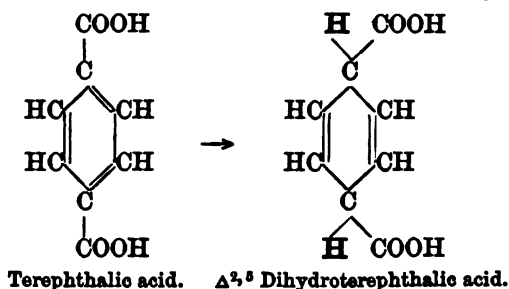
Baeyer found that on reducing the phthalic acids with sodium amalgam in alcoholic solution the hydrogen atoms attach themselves to the α -carbon, i.e. to the carbon which carries the carboxyl group.

¹ *Annalen*, 1890, 258, 145; 1892, 269, 145.

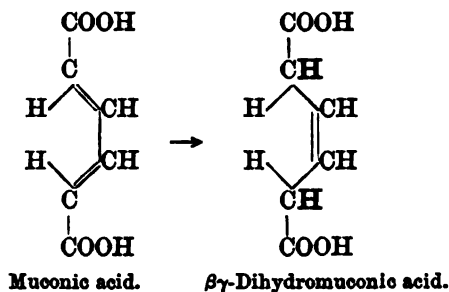
² *Annalen*, 1898, 276, 255.

³ *Annalen*, 1888, 245, 108; 1889, 251, 257; 1890, 258, 1.

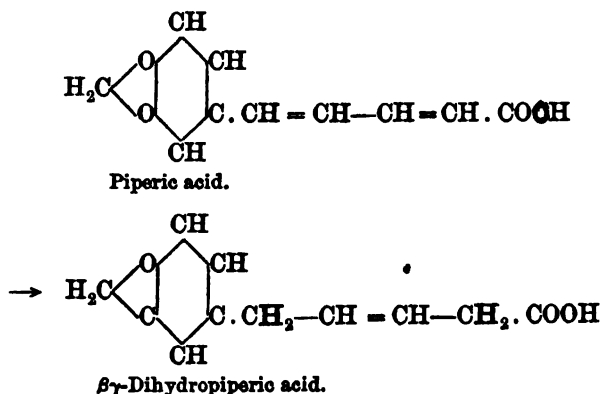
The same thing was observed in the case of unsaturated open-chain acids, like muconic and piperic acid, and was ascribed by Baeyer to the electro-negative character of the α -carbon.¹ For example, the first reduction product of terephthalic acid is the $\Delta^{2,5}$ dihydro acid,



whilst muconic acid is converted into $\beta\gamma$ -dihydromuconic acid,



and piperic acid yields $\beta\gamma$ -dihydropiperic acid.

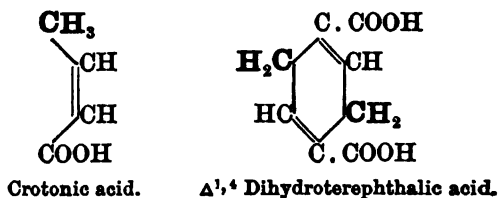


Baeyer explained the process as follows: 'Reduction only occurs if hydrogen ions can penetrate the molecule. The number is con-

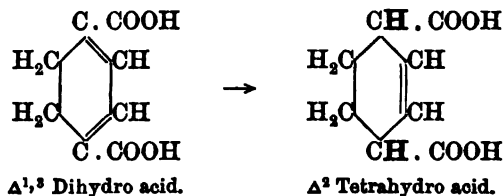
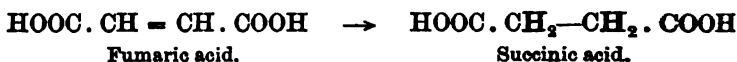
¹ *Annalen*, 1889, 251, 265.

ditioned by the number of negative groups, which makes reduction possible—in the present instance, by the carboxyl in conjunction with the double bond.'

If, however, the double bond is in proximity to a positive group— CH_2 or CH_3 —as in crotonic or $\Delta^{1,4}$ dihydroterephthalic acid, reduction is very much impeded,



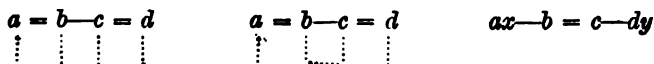
whilst fumaric and $\Delta^{1,3}$ dihydroterephthalic acid readily undergo reduction to succinic and Δ^2 tetrahydroterephthalic acid respectively.



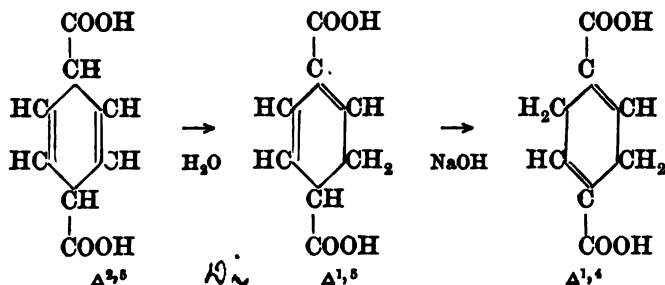
A very different explanation of the process has been advanced by Thiele,¹ which will be briefly outlined, inasmuch as it forms the basis of a new view of the structure of benzene, to be presently discussed. Thiele supposes that each doubly linked atom, in addition to its ordinary bonds, is provided with a partial valency, and it is by means of this partial valency that union with other atoms is first effected. Moreover, the partial valencies of two adjoining atoms can unite or become 'conjugated', which causes them to lose their activity. Thus, in a system containing two pairs of doubly linked atoms separated by a single bond and known as a 'conjugated' system, the partial valencies of the middle pair can unite and thus become inactive, leaving the two end atoms free to combine. When this occurs, the bonds between the middle pair of atoms are transposed into an ordinary double bond. The stages in the process may be

¹ *Annalen*, 1899, 306, 125.

represented by the following scheme, in which the dotted lines indicate the partial valencies:

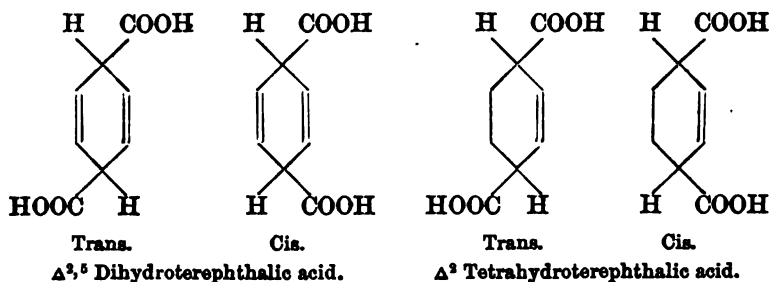


The theory explains the addition of only two hydrogen atoms and the positions which they occupy on reducing such compounds as muconic, piperic, and terephthalic acid, &c. To return now to the reduction of terephthalic acid, the first product is the $\Delta^{2,5}$ dihydro acid. No further reduction takes place until a double bond has been displaced towards the α -carbon, a process which has already been discussed (p. 178), and may be accomplished in the case of $\Delta^{2,5}$ dihydroterephthalic acid in two steps, the first by boiling with water which gives the $\Delta^{1,5}$ isomer, and the second by boiling with dilute solutions of caustic alkalis which transforms the latter into the $\Delta^{1,4}$ acid.



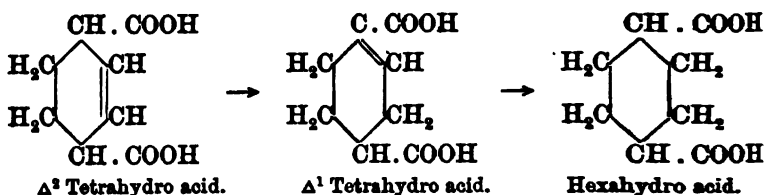
Tetrahydroterephthalic acids.

The $\Delta^{1,5}$ acid can now be reduced and yields Δ^2 tetrahydroterephthalic acid. Both the $\Delta^{2,5}$ and Δ^2 acids exist in stereoisomeric forms, each pair bearing a similar relation to one another as maleic acid bears to fumaric acid (p. 129).

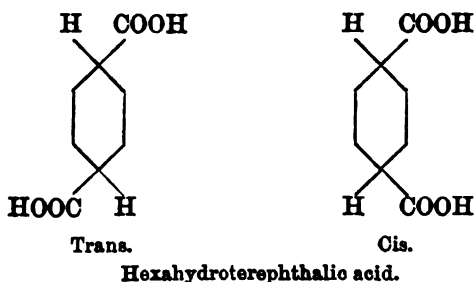


The action of caustic alkalis on the Δ^2 acid causes the double

bond to shift to the Δ^1 position, and the acid, thus produced, yields hexahydroterephthalic acid on reduction.

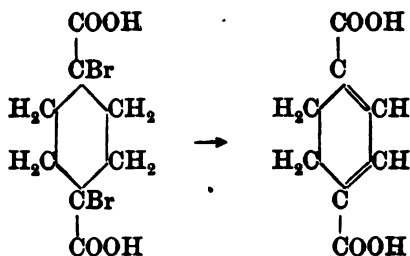


The hexahydro acid also exists in stereoisomeric forms which may be represented by the following formulae (p. 129):

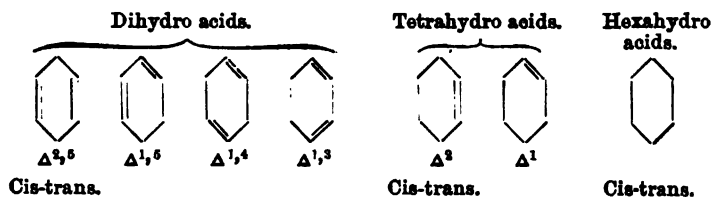


The last of the series of possible isomers is derived from the $\alpha\alpha_1$ -dibromohexahydro acid already described (p. 449), from which alcoholic potash removes two molecules of hydrogen bromide.

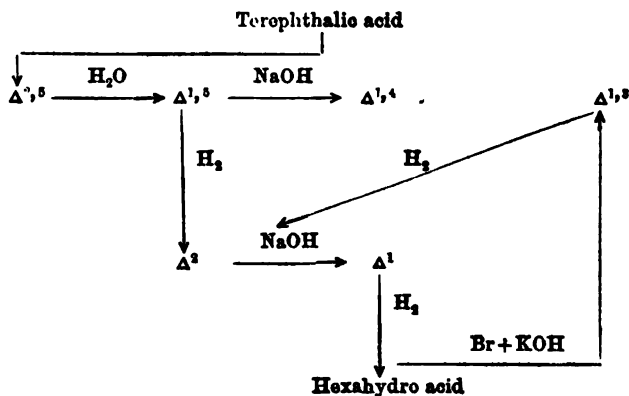
The product is $\Delta^{1,3}$ dihydroterephthalic acid.



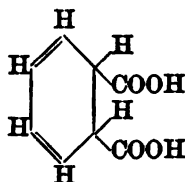
There are other ways in which reduction may be effected, such as the action of zinc dust and acetic acid on the hydrogen bromide additive compounds, but it is unnecessary to enter into further detail. It is sufficient for the present purpose to indicate the manner in which the complete series of reduced terephthalic acids have been prepared. They may be tabulated as follows:



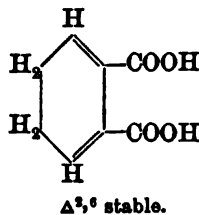
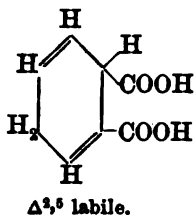
Their relation to one another is indicated in the following table.



Similar results were obtained with phthalic and isophthalic acids, with α and β naphthoic acids, benzoic acid, &c., all of which form a series of hydro acids. Thus, phthalic acid, in accordance with the rule by which the hydrogen attaches itself to the α -carbon, gives in the first place a $\Delta^{3,5}$ dihydro acid, having the following structure :

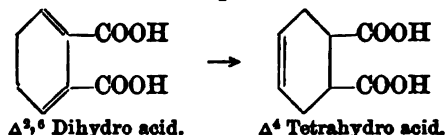


This, by the shifting of the double bond, forms the $\Delta^{2,6}$ dihydro acid, the intermediate $\Delta^{2,5}$ acid being probably very unstable.¹

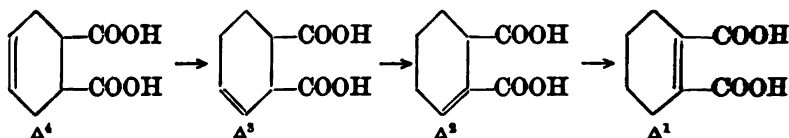


¹ See G. Abati, *Abstr. Chem. Soc.*, 1906, 1, 959; 1907, 1, 419.

The latter undergoes reduction, but in an abnormal fashion, the hydrogen probably attaching itself not to the α -carbons but to those in positions 3 and 6 according to Thiele's rule, and the double link shifts at the same time to the Δ^4 position.

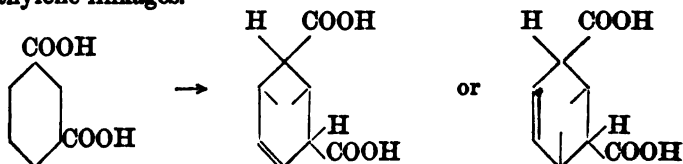


The latter on boiling with caustic soda solution may be converted successively into the Δ^3 , Δ^2 , and Δ^1 acids.¹

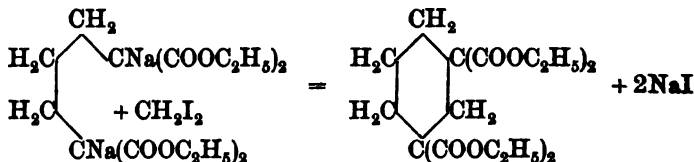


The symmetrically constituted acids exist, like the analogous terephthalic acids, as *cis* and *trans* isomers.

In the case of isophthalic acid great difficulty is experienced in effecting reduction, and Baeyer explains this by the fact that the attachment of the hydrogen to the α -carbons prevents the formation of ethylene linkages.



Nevertheless two tetrahydroisophthalic acids have been obtained by direct reduction², and also a hexahydro acid in *cis* and *trans* forms³, whilst a dihydro acid and two other tetrahydro acids have been prepared by indirect methods. In this connection should also be mentioned the important synthesis of *cis* and *trans* hexahydroisophthalic acid by Perkin, jun.,⁴ from di-sodium pentane tetracarboxylic ester and methylene iodide.



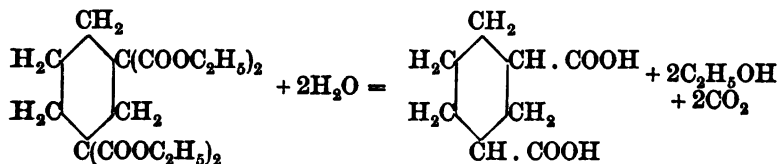
¹ *Annalen*, 1890, 258, 167, 212.

² Perkin, Pickles, *Trans. Chem. Soc.*, 1905, 87, 298, 841.

³ Baeyer, *Annalen*, 1892, 269, 178, 195.

⁴ Perkin, *Trans. Chem. Soc.*, 1891, 59, 808.

The latter on hydrolysis loses carbon dioxide and gives the hexahydro acids.



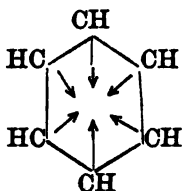
This synthesis, as previously mentioned, is a clear indication of the ring structure of benzene and its reduction products.

Aliphatic Character of Hydrocyclic Compounds. We have already perceived the close analogy which subsists between the hydrophthalic acids and the saturated and unsaturated acids of the aliphatic series, their behaviour on bromination, the position taken up by the hydrogen on reduction, the shifting of the double bond, &c. This analogy may be extended, for the double bond of the di- and tetra-hydro acids possesses the unsaturated character of true ethylene linkages. These compounds unite readily with hydrogen bromide, as well as with bromine, and the hydrogen bromide and bromine additive compounds lose hydrogen bromide on treatment with alcoholic potash and become unsaturated. Moreover the di- and tetra-hydro acids show the general behaviour of unsaturated fatty acids in rapidly decolourising alkaline permanganate in the cold. The olefinic character of the partly reduced acids is reproduced in the di- and tetra-hydro benzenes which resemble true olefines, whereas the saturated ring structures as represented by cyclohexane and other cycloparaffins possess the characteristic properties of the paraffins.

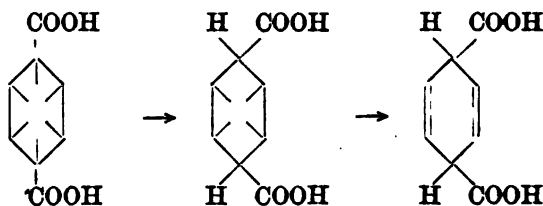
In marked contrast to these compounds stands benzene with many of its substitution products. Terephthalic acid, for example, unlike the di- and tetra-hydro acids, is neither oxidised by permanganate in the cold nor combines to form additive compounds with bromine or hydrogen bromide. How is this difference in chemical behaviour to be reconciled with the presence of three ethylene linkages in benzene? This is the question to which Baeyer has tried to find an answer in the results of his research on the reduction products of the phthalic acids. Adopting a suggestion of Armstrong,¹ he supposes that the fourth carbon valency is directed towards the centre of the benzene ring though not actually linked to its opposite neighbour in the para position, as represented in Claus's original

¹ *Trans. Chem. Soc.*, 1887, 51, 264 (footnote).

formula. This *centric bond* is not a real but a potential bond exerting a directive force or pressure towards the centre of the molecule. The formula is known as the *centric formula*, and can be pictured by the following diagram, in which the centric bonds appear as arrows:

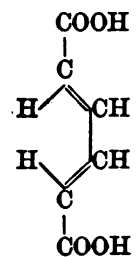


Baeyer does not regard this formula as representing the structure of all benzene derivatives. For certain compounds, such as phloroglucinol, which are readily oxidised by permanganate, the Kekulé formula is retained. 'The benzene nucleus,' he says, 'can exist in two forms which can be regarded as tautomeric in the sense that a definite structure is attached to each individual derivative.'¹ The centric formula enables the reduction of the phthalic acids to be represented by a simple mechanical device. Thus, the first two hydrogen atoms attach themselves to the two α -carbons, and thereby remove two centric bonds in the para position. The result is the linking up of the remaining two pair of bonds forming true ethylene linkages.

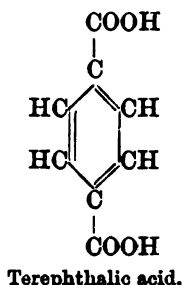


Baeyer nevertheless recognizes that the Kekulé formula is capable of expressing equally well the formation of $\Delta^{2,5}$ dihydroterephthalic acid; for the behaviour of muconic acid on reduction furnishes an exactly parallel case with that of the attachment of the two hydrogen atoms to the α -carbons in terephthalic acid and the consequent shifting of the double bond.

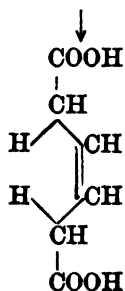
¹ *Annalen*, 1892, 269, 188.



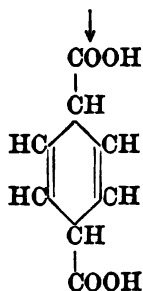
Muconic acid.



Terephthalic acid.

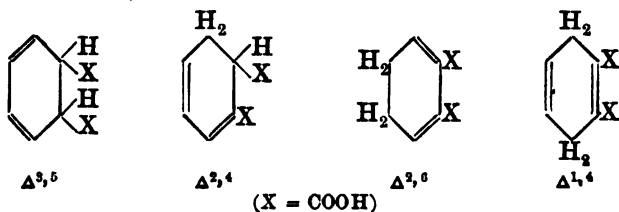


Dihydromuconic acid.



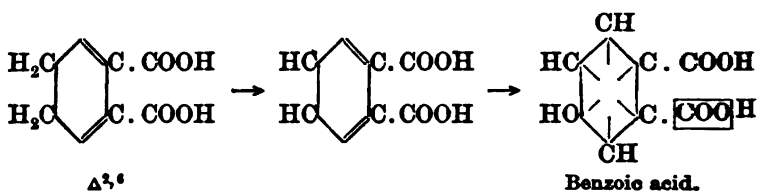
Dihydroterephthalic acid.

Baeyer¹ in fact admitted that the structure of benzene derivatives could not be determined by their behaviour on reduction. He therefore turned to the reverse process—the oxidation of the hydro acids—and sought for evidences of structure in the behaviour of these compounds. It must be confessed that the results of this inquiry appear incomplete and unconvincing. Baeyer perceives in the fact that the $\Delta^{3,5}$, $\Delta^{2,4}$, and $\Delta^{2,6}$ dihydrophthalic acids give benzoic acid on oxidation,

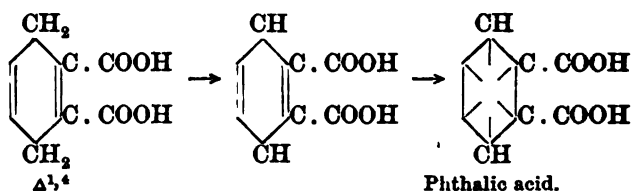


whilst the $\Delta^{1,4}$ acid gives phthalic acid, a shock (Erschütterung) to the α -carbon in the three former cases, which causes it to lose carbon dioxide, this effect being associated with the change from ethylene to centric linkages thus:

¹ *Annalen*, 1892, 269, 178.

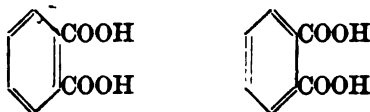


The formation of benzoic acid from the $\Delta^{2,6}$ dihydro acid, in which oxidation does not directly affect the α -carbons, is accounted for by the carbons in the para position to the α -carbons being involved in the change, whereas oxidation of the $\Delta^{1,4}$ acid neither directly nor indirectly touches the α -carbons.

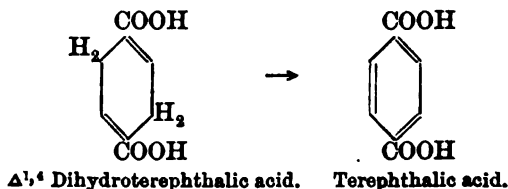


Brühl,¹ in a careful examination of this theory, asks why only one molecule instead of two molecules of carbon dioxide is removed from the $\Delta^{2,6}$ acid, and (he also might have added) from the $\Delta^{2,5}$ dihydro acid, both of which are symmetrical structures.

It might be urged in favour of Kekulé's formula that, of the two possible phthalic acids, only the first is stable.



This would be formed by the oxidation of the $\Delta^{1,4}$ dihydro acid, whilst the second should appear when the $\Delta^{2,6}$ acid is oxidised. The loss of carbon dioxide in the second case might be attributed to the shock attending the rearrangement of double linkages; but as $\Delta^{1,4}$ dihydroterephthalic acid yields terephthalic acid on oxidation, when likewise a change in the double bonds must be assumed to occur, this argument is untenable.



¹ *Journ. prakt. Chem.*, 1894 (2), 49, 229.

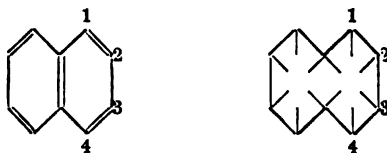
Brühl in his criticism has sought to explain the different chemical behaviour of the dihydro acids on the very simple basis of their difference of stability, and such a view has the advantage of being independent of any structural hypothesis. At the same time he apparently fails to perceive that by avoiding any reference to structure as affecting stability he is 'begging the question'.¹

Evidence of Physical Properties. The data afforded by the values of the melting-points and solubilities of phthalic acid and its anhydride appear to be the mean of those calculated by Baeyer² for the two formulae:

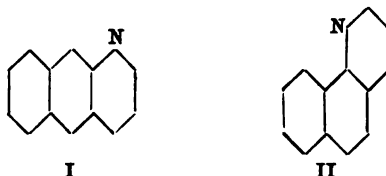


and have been used as evidence in favour of the centric formula; but when it is considered that the calculated constants are derived from the somewhat artificial analogies instituted between the isomeric di-, tetra-, and hexa-hydro acids, and that, in addition, we are profoundly ignorant of any connection between these physical constants and structure, the evidence cannot be regarded as entirely trustworthy. Of greater interest are the optical and thermo-chemical

¹ Marckwald, *Annalen*, 1893, 274, 331; 1894, 279, 14, sees in the different behaviour of amino-naphthalenes and amino-quinolines, when submitted to the reactions of Skraup and Doebner-Miller, a confirmation of Kekulé's hypothesis; for according to the Erlenmeyer formula for naphthalene and the Körner formula for quinoline (see p. 551) the positions 1.2 and 3.4 are different from 2.3, whilst in the centric formula they are equivalent.



With an amino group in position 1 or 2 the attachment of a pyridine group by the above reactions never produces a compound of the symmetrical type (I) but always of the unsymmetrical type (II).



² *Annalen*, 1892, 269, 186.

constants of benzene and its derivatives. From determinations of the molecular refraction and dispersion of benzene and di-, tetra-, and hexa-hydrobenzene, Brühl has arrived at the conclusion that three double linkages are present in benzene, since diallyl, hexylene, and hexane show a corresponding increment for each double bond. The following table is taken from Brühl's paper.¹

	Density at 20°/4	Refractive Index at 20°	Mol. Vol. at 20°	Sp. Ref. $\frac{n^2-1}{(n^2+2)d}$	Mol. Ref. $\left(\frac{n^2-1}{n^2+2}\right)\frac{M}{d}$	
					H_a	D
Benzene	0.8799	1.4967	88.65	0.8824	25.98	26.13
Dihydrobenzene	0.8478	1.4699	94.86	0.8291	26.83	26.51
Tetrahydrobenzene	0.8102	1.4485	101.21	0.8277	26.87	27.01
Hexahydrobenzene	0.790	1.426	107.2	0.8255	27.56	27.66 ²
Dipropargyl	0.8049	1.4402	96.91	0.8278	25.57	25.74
Diallyl	0.6880	1.3981	119.18	0.8509	28.77	28.96
Hexylene	0.6825	1.3989	123.08	0.8506	29.45	29.61
Hexane	0.6608	1.3784	180.25	0.8454	29.70	29.84

In order to institute a comparison between the aliphatic and aromatic series we may either take differences between successive or between corresponding members of each series.

	M_D	Δ		M_D	Δ
Benzene	26.18	.38	Diallyl Hexylene Hexane	28.96	
Dihydrobenzene	26.51	.50		29.61	.65
Tetrahydrobenzene	27.01	.65		29.81	.23
Hexahydrobenzene	27.66				

	M_D	Δ
Diallyl	28.96	2.45
Dihydrobenzene	26.51	
—		
Hexylene	29.61	2.60
Tetrahydrobenzene	27.01	
—		
Hexane	29.84	2.28
Hexahydrobenzene	27.66	

¹ *J. prakt. Chem.*, 1894 (2), 49, 250.

² The value for hexahydrobenzene represents the mean of those calculated from three independent sets of data which fluctuate between 27.91 and 27.31.

In examining the figures in the first of the above tables, it is clear that the differences among members of the same series are very small; for the molecular refractions are made up of two opposed factors, namely, the index of refraction which forms a decreasing series, and the molecular weights which form an increasing series from the less to the more hydrogenated compounds. When, in addition to this, it is considered that the difference between the minimum and maximum value calculated for hexahydrobenzene nearly covers the whole difference between tetra- and hexa-hydrobenzene, the significance of these figures becomes very small. The larger differences between the molecular refractions of members of the corresponding series is clearly due to ring formation. Very little reliance can therefore be placed on the direct evidence which molecular refractions afford of three double linkages in benzene. On the other hand, it seems clear that there is no sudden change of structure between benzene and its reduction products, such as occurs between hexane and hexahydrobenzene, or between dipropargyl with its two treble linkages, and diallyl with its pair of double bonds.

From the results of molecular volume determinations Schiff¹ concluded that benzene contains nine single carbon linkages; but this view was subsequently opposed by Lossen and Zander,² and by Horstmann,³ who gave their verdict in favour of Kekulé's formula from the results of a much more complete series of observations. The conclusions derived from thermo-chemical data are very conflicting. Thomsen's⁴ determinations of the heats of combustion led him at first to conclude that benzene contains nine single bonds, a view which was also shared by Horstmann,⁵ but he afterwards transferred his adherence to Kekulé's formula. Stohmann, on the other hand, from the evidence of a much more comprehensive series of observations, arrived at Thomsen's original conclusion that 'three equivalent double bonds cannot be present in the benzene nucleus. The bonds are most firmly attached in benzene itself, and more loosely in the di- and tetra-hydro compounds, reaching again a high degree of stability in hexahydrobenzene which is, however, unequal to that of the original nucleus.' The following are the constants for the heats of combustion of benzene and its reduction products obtained by Stohmann and Langbein:⁶

¹ *Annalen*, 1883, 220, 308.

² *Annalen*, 1884, 225, 109.

³ *Ber.*, 1887, 20, 766.

⁴ *Ber.*, 1880, 12, 1806; *Thermochem. Untersuch.*, 1886, vol. iv.

⁵ *Ber.*, 1888, 21, 2211.

⁶ *J. prakt. Chem.*, 1898 (2), 48, 447.

	Cal.	Δ
Benzene	779.8	68.2
Dihydrobenzene	848.0	44.0
Tetrahydrobenzene	892.0	41.2
Hexahydrobenzene	938.2	58.0
Hexane	991.2	

The differences correspond closely with those of terephthalic acid and its reduction products.¹

	Δ
Terephthalic acid	> 68.7 Cal.
Dihydro acid	> 45.8 "
Tetrahydro acid	> 45.8 "
Hexahydro acid	> 54.8 "
Sebacic acid	

It seems not improbable, therefore, that benzene and terephthalic acid are similarly constituted.

As the heat of combustion of H_2 is 69 Cal., it follows that during the graduated reduction of benzene 'the formation of dihydrobenzene utilizes almost the whole of the energy of the hydrogen molecule; in the second stage of reduction there is an excess of energy amounting to 25 Cal. in the initial system, and in the third an excess of 27.8 Cal., whereas in the final stage, where the benzene nucleus is dissolved, the energy of the initial system only amounts to 11 Cal.'

From this Stohmann concludes that the 'jump' between the first and second terms of the series compared with the two following, as well as between the fourth and fifth, indicates a fundamental difference of structure between benzene and its di- and tetra-hydro derivatives, and also between tetrahydro- and hexahydro-benzene, which led him, as we have seen, to reject the Kekulé formula. These conclusions have been contested by Brühl,² who adopts an entirely different attitude in the interpretation of Stohmann's results. He shows from Stohmann's own observations that substantial differences in heats of combustion are frequently found among isomeric and even stereoisomeric compounds, and that these effects mainly depend on the stability of the compounds in question. The unequal differences observed in the heats of combustion of the different states of hydrogenation of benzene depend on the stability of the individual compounds. When a body passes from a less to a more stable condition it loses heat energy, and, according to Brühl, the differences obtained by Stohmann are fully accounted for by the greater stability of benzene and hexahydrobenzene, compared

¹ The isomeric di- and tetra-hydro acids differ slightly among themselves.

² *J. prakt. Chem.*, 1894 (2), 49, 260.

with that of the intermediate compounds. This stability of the benzene molecule is attributed to the symmetry of the Kekulé formula. The argument might be applied with equal force to the diagonal formula which is even more symmetrical.

In conclusion it must be admitted that the evidence of physical properties has thrown little new light on the benzene problem.¹

Space Formulae for Benzene. Whatever view has been taken of the structure of benzene, it has sooner or later found expression in a space formula. Representing the carbon atoms by tetrahedra, Kekulé's formula will assume the following form:

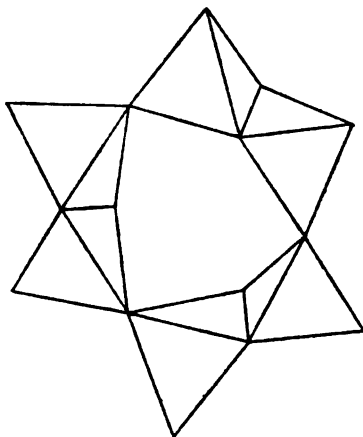


FIG. 32. Kekulé's space formula.²

It will be noticed that the hydrogen atoms lie in the same plane with the carbon atoms, and consequently, however dissimilar the groups replacing hydrogen may be, no asymmetric molecule can be formed. Also, the breaking of a double bond by reduction obviously involves two carbon atoms.

In Baeyer's space formula³ the tetrahedra are arranged in a compact ring, each with a face on the same horizontal plane, and with the hydrogen linkages pointing upwards, so that the hydrogen atoms lie in a parallel plane with the carbon atoms.

¹ A recent study of the magnetic rotation of hexatriene by Perkin, sen., appears to confirm the Kekulé formula. *Trans. Chem. Soc.*, 1907, 91, 806.

² This and the following figures are taken from Graebe, *Ber.*, 1902, 35, 526.

³ *Annalen*, 1888, 245, 128; see also Erlenmeyer, jun., *Annalen*, 1901, 316, 57.

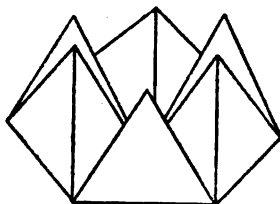


FIG. 33. Baeyer's space formula.

A similar arrangement to Baeyer's has been suggested by Marsh, Vaubel,² and others.

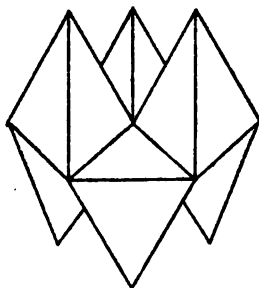


FIG. 34. Vaubel's space formula.

In this formula the tetrahedra are arranged alternately above and below the middle plane so that three hydrogen atoms lie in one plane, three in another, and the six carbon atoms occupy two parallel planes between them. In both Baeyer's and Vaubel's space formulae, hydrogenation does not necessarily involve more than one carbon atom at a time.

Another space formula of a very different type has been proposed by Sachse.³ It is formed by cutting away two parallel faces of an octahedron and superposing tetrahedra on the remaining six faces.

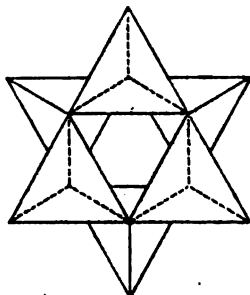


FIG. 35. Sachse's space formula.

¹ *Phil. Mag.*, 1888, 26, 426.

² *J. prakt. Chem.*, 1891, 44, 187; 1894, 49, 308; 50, 58.

³ *Ber.*, 1888, 21, 2580; 1890, 23, 1868.

The model is easily made by cutting a piece of thin card of the following shape (Fig. 86), nicking it and bending it over where the dotted lines are drawn, and fastening the ends, when it will form an octahedron with two parallel faces missing.

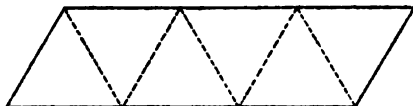


FIG. 86.

The tetrahedra are made in a similar way by cutting out an bending pieces of the following shape (Fig. 87).

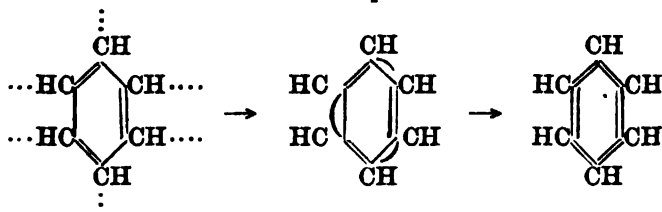


FIG. 87.

Each of the tetrahedra should be placed on one of the six faces of the octahedron, which will assume the form shown in Fig. 85, but each tetrahedron should be fastened only by an edge (with gummed paper) to the left-hand vertical edge of the face so as to enable the process of hydrogenation to be realized. In Sachse's model the hydrogen atoms lie in two parallel planes, whilst the carbon atoms occupy a parallel plane between them. Also, the hydrogenation of one carbon atom does not necessarily involve that of a second carbon atom.

Sachse proposed the formula with the object of representing the most stable, compact, and symmetrical grouping of six tetrahedra, and it has received the support of Brühl¹ and of Thiele.²

On the theory of conjugated systems of double bonds, to which reference has already been made (p. 452), Thiele³ has pointed out that benzene represents a twofold conjugated system. Supposing that each carbon atom of benzene possesses a partial valency, and that, as previously explained, adjoining partial valencies neutralize one another or become conjugated, the result will be equivalent to a potential double link between each pair of carbon atoms.

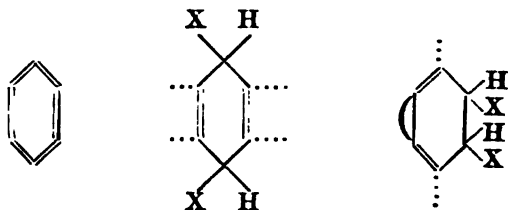


¹ *J. prakt. Chem.*, 1894 (2), 49, 236; *Zeit. phys. Chem.*, 1898, 11, 214.

² *Annalen*, 1901, 319, 186.

³ *Annalen*, 1899, 306, 125.

Such an arrangement will, according to Thiele, explain the stability of benzene, its difference from ordinary olefinic compounds with three double bonds, and, more especially, its behaviour on reduction; for if hydrogen is added in the ortho or para positions, as in the reduction of phthalic or terephthalic acid, the conjugated double bond is transformed into an ordinary olefinic linkage.



The first acquires four partial valencies, and can consequently unite with four atoms of bromine, whilst the second is endowed with two and can therefore only form a dibromo-derivative, which, as Thiele points out, is in complete agreement with Baeyer's observations. Various other arguments are brought forward in support of this formula for which the original paper must be consulted.

Thiele adopts Sachse's formula as the effective space representation of his view of the structure of benzene. When examined it will be observed that each carbon atom is linked by two pairs of bonds to its neighbours and by one to hydrogen. Each carbon is apparently provided with five bonds; but as two pairs are conjugated they are to be regarded, it is presumed, like centric valencies, that is, as modified in character.

It is not our intention to discuss the arguments for and against each of the above space formulæ; but it may be observed that any formula to be satisfactory must represent in a simple fashion the symmetry of the molecule, the process of hydrogenation, the anhydride formation of ortho compounds and the relation to naphthalene and other multinuclear hydrocarbons. These points have been discussed in detail by Graebe,¹ who finds that Kekulé's formula is the only one which meets the many demands made upon it. It may be stated also that, with the single exception of Kekulé's formula, there is one inherent defect in all. Unless the carbon and hydrogen atoms lie in the same plane, the replacement of two hydrogen atoms by different groups in the ortho or meta position leads at once to asymmetry and to the possibility of optical enantiomorphs. It has already been pointed out in connection with Ladenburg's formula (p. 446) that neither among artificial nor

¹ *Ber.*, 1902, 35, 526.

natural products have substituted benzene derivatives of this character been observed.

In reviewing the more important evidence which has been accumulated on the subject of the benzene formula there seems to be no static representation which explains so large a number of facts as Kekulé's formula. When it has been proved that simple benzene derivatives can exist in optically active forms it will be time to reconsider the position.

Dynamic Formulae for Benzene. At a very early period in the history of the benzene formula, Kekulé put forward a dynamic hypothesis to explain the equivalence of the two ortho positions (p. 447). This was followed by Knorr's oscillation formula, in which only the hydrogen atom was assumed to oscillate between each pair of carbon atoms. Knorr's view, which bears a close resemblance to Laar's theory of tautomerism, was the direct consequence of the observation establishing the identity of methyl pyrazole obtained from two different phenylmethyl pyrazoles, and has already been discussed (p. 186). In 1897 a new dynamic formula was proposed by Collie,¹ in which the carbon groups as a whole are supposed to rotate as well as change their relative positions. Without a model it is impossible to describe the evolutions of this mobile system; but it is claimed that it represents in turn the Kekulé and centric arrangement as phases of the one formula. Latterly, the study of the absorption bands in the ultra-violet region of the spectrum has led to views on the dynamical condition of benzene, which promise a very interesting development. According to Hartley,² six, or according to Baly and Collie,³ seven, distinct absorption bands are produced by benzene. These bands are accounted for by synchronous oscillations of the molecule, in much the same way as a tuning-fork vibrates in response to a note of definite pitch. The nature of these molecular vibrations are, however, differently interpreted by the two observers. Hartley supposes the carbons to be rotating and alternately passing through a double and single (or centric) link phase. If the passage from single to double linking produces a band, the first phase which involves the making of three double links will produce three bands and the second phase another three bands, making six together, though it is not obvious why the same recurrent process should produce six sets of oscillation frequencies. Baly and Collie take a different view. The oscillations are connected with dynamic

¹ *Trans. Chem. Soc.*, 1897, 71, 1018.

² *Trans. Chem. Soc.*, 1905, 87, 1822.

³ *Trans. Chem. Soc.*, 1905, 87, 1832.

change involved in the making and breaking of the links between one or more pairs of carbon atoms.

Now, it is possible to produce from the six carbon atoms, constituting benzene, seven combinations of one, two, and three pairs of carbon atoms. If making and breaking of links occurs between these pairs, it will set up vibrations in the benzene ring which correspond to the seven absorption bands, and these vibrations are compared with an expanding and contracting elastic ring.¹

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¹ *Trans. Chem. Soc.*, 1906, 89, 524.

CHAPTER XIII

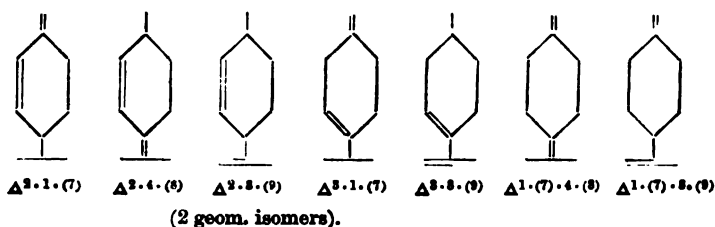
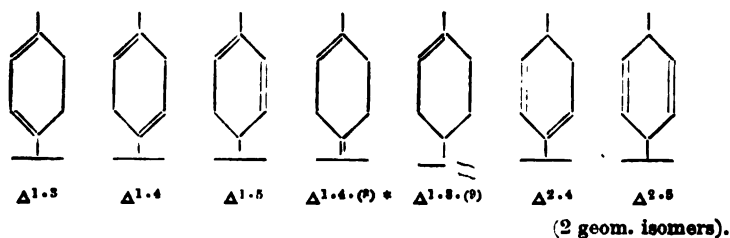
THE TERPENES AND CAMPHORS

The Terpenes. The terpenes are hydrocarbons of the formula $C_{10}H_{16}$, which are found widely distributed and in considerable quantities in the *essential oils* of plants. They occur in different parts of the plant, sometimes singly, sometimes two or more together, and very frequently associated with *sesquiterpenes* $C_{15}H_{24}$, and with closely allied compounds containing oxygen, such as *thymol* and *carvone*, $C_{10}H_{14}O$, *cineol*, *fenchone*, *thujone*, and *camphor*, $C_{10}H_{16}O$, *terpineol* and *borneol*, $C_{10}H_{18}O$, *menthol*, $C_{10}H_{20}O$, &c. A more complete account of these oils is given in the section on natural and artificial perfumes (p. 529).

The terpenes have been the subject of careful and elaborate investigation during the last twenty years, chiefly at the hands of Prof. Wallach, who has devoted himself with signal success to unravelling the tangled web of facts scattered through the literature of the subject, and to developing methods of identifying the members of this large family of isomeric compounds. He has, moreover, traced the relations which subsist between them, and brought our knowledge to a point at which the difficult problems of structure may be considered to be within measurable distance of solution.

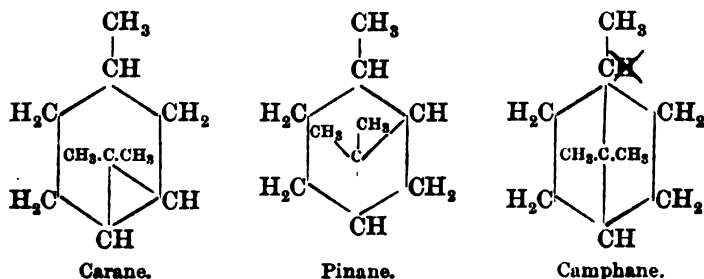
Properties of the Terpenes. More than a dozen distinct compounds of the formula $C_{10}H_{16}$ are at present known; among which are *d*- and *l*-*limonene* and the racemic form of *dipentene*, *terpinolene*, *terpinene* and *phellandrene*, *d*-*sylvestrene*, and its inactive form, *carvestrene*, *d*-*l*-*pinene*, *d*-*l*-*camphene*, *bornylene*, *fenchene*, and *thujene*. With the exception of *terpinolene*, *fenchene*, *bornylene*, *carvestrene*, and *thujene*, they are found in nature. *Camphene* and *bornylene* are solids at the ordinary temperatures, but the remainder are liquids which distil unchanged at temperatures varying from 155° to 185° . They have a high specific refraction (1.46–1.47) and a low specific gravity (0.84–0.86).

They appear to be all cyclic compounds standing midway as to properties between benzene hydrocarbons and the olefines. On the one hand they form additive compounds with the halogens, halide



* The bracketed numbers indicate the second carbon attachment of the double bond outside the nucleus.

Compounds of this class are naturally able to combine with two molecules of halogen, halide acid, &c. Thus, limonene forms a dihydrobromide, $C_{10}H_{16} \cdot 2HBr$, with hydrogen bromide, and a tetrabromide, $C_{10}H_{16}Br_4$, with bromine. The second group of bi-cyclic compounds can, on the other hand, only unite with one molecule of halogen and halide acid, and, for this and other reasons to be presently discussed, they are assumed to have a bridged-ring structure. Three bridged rings are now recognized as the basis of the second group, and the corresponding saturated hydrocarbons, $C_{10}H_{18}$, are known respectively as *carane*, *pinane*, and *camphane*.



It follows that the terpenes derived from them will contain one double bond only, and may be described as *carene*, *pinene*, and *camphene*. The position of the double bond will be discussed in the sequel. It is clear, however, that the opportunities for isomerism are more restricted than in the case of the menthadienes. With

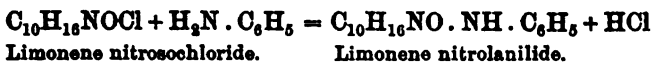
this brief account of the system of classification and nomenclature, we will pass at once to the study of the properties and structure of the individual terpenes, beginning with the simpler class of menthadienes.

MONO-CYCLIC TERPENES (MENTHADIENES).

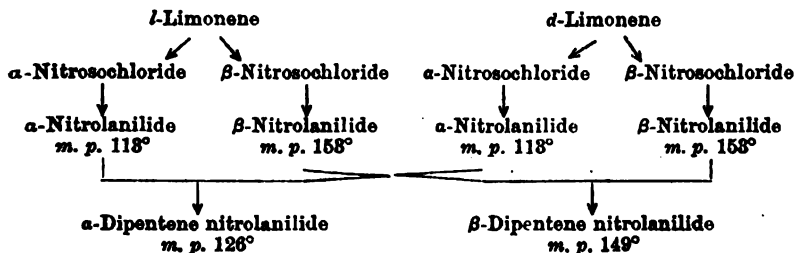
d-l-Limonene (Dipentene). *D*- and *l*-limonene and the racemic form of dipentene are among the most widely distributed constituents of essential oils. They possess the characteristic smell of lemon. The *d*-compound is found in oil of lemons, neroli (from orange flowers), orange (from the rind), bergamot, limette, caraway, dill, &c.

The *l*-compound is less common and is a constituent of pine-needle oil from *Abies alba*, Russian and American spearmint oil, American peppermint oil, &c., whilst the inactive dipentene is found in pine-needle oil, citronella oil, oil of cubebs, &c. It is also formed by mixing the two active limonenes, or by racemising them singly at a high temperature. Many other terpenes yield dipentene on continued heating, a fact which may explain its presence in the products of the dry distillation of rosin and caoutchouc. Another interesting source of dipentene is pinene, the chief constituent of ordinary American turpentine oil, from which it may be obtained directly by the action of alcoholic sulphuric acid or, indirectly, by the aid of moist hydrogen chloride, which transforms pinene into the dihydrochloride of dipentene, $C_{10}H_{16} \cdot 2HCl$. The explanation of these changes will be discussed under pinene (p. 492). Dipentene can also be obtained from the closely allied substances *terpineol* (m. p. 35°) and *cincol*, which are described later. Dipentene is usually separated and purified by conversion into the crystalline dihydrochloride (by passing gaseous hydrogen chloride into the liquid), from which the terpene is regenerated by boiling the hydrochloride with anhydrous sodium acetate dissolved in acetic acid. This method cannot be applied to the limonenes, for they are racemised in the process. Pure limonene is purified by conversion into the crystalline tetrabromide, $C_{10}H_{16}Br_4$, from which it is liberated by reduction with zinc dust and alcohol. *l*-Limonene can also be obtained from active dihydrocarveol by the xanthic ester method of Tschugaeff, which is described later (p. 504). Highly characteristic of dipentene and the limonenes are the compounds with nitrosyl chloride. They are crystalline substances of the formula $C_{10}H_{16}NOCl$, which are best obtained by adding amyl nitrite dissolved in glacial acetic acid to the terpene and acidifying with strong hydrochloric acid. As the addition of

nitrosyl chloride introduces a new asymmetric carbon into the molecule, as will presently appear, it is scarcely surprising that each of the limonenes, as well as dipentene, should yield two products, α - and β -nitrosochlorides. By the action of aniline on each of the six compounds a different nitrolanilide is obtained.



The α - and β -*d*-nitrosochlorides will be enantiomorphous with the α - and β -*l*-nitrosochlorides, so that by mixing equivalents of *d*- and *l*- α -nitrosochloride and *d*- and *l*- β -nitrosochloride, the two dipentene compounds are obtained. The same is of course true of the nitrolanilides.



In addition to a nitrosochloride compound, dipentene forms a nitrosate, $\text{C}_{10}\text{H}_{16}\text{NO} \cdot \text{ONO}_2$, by the combined action of nitric acid, amyl nitrite, and acetic acid.

Structure of Limonene (Dipentene). In attempting to ascertain the constitution of these compounds it will be necessary in the first place to describe certain other substances to which they are related.

The chief interest centres round the structure of carvone and terpineol. Both compounds are found in nature accompanying the terpenes, and both are closely related to dipentene, the limonenes, and terpinolene.

Carvone, $\text{C}_{10}\text{H}_{14}\text{O}$, formerly known as carvol, is found as the *d*-form in dill and caraway oil, and as the *l*-modification in spearmint and kuromoji oil, and possesses the characteristic smell of caraway oil. It is isolated and purified by conversion into a curious crystalline compound which it forms with hydrogen sulphide, $(\text{C}_{10}\text{H}_{14}\text{O})_2\text{H}_2\text{S}$.

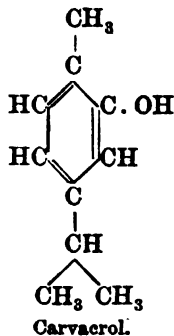
It is a ketone and forms a carboxime, $\text{C}_{10}\text{H}_{14} \cdot \text{NOH}$, which Goldschmidt and Zürrer¹ found to be identical with the nitroso-

¹ Ber., 1885, 18, 2220.

limonene obtained by Tilden and Shenstone¹ by the action of alcoholic potash on the nitrosochloride,



Now carvone is easily converted by heating with phosphoric acid and with certain other reagents into the isomeric *carvacrol*, the structure of which is known. It is a hydroxy *p*-cymene of the formula:



We may therefore assume that in this reaction an isomeric change occurs in carvone, whereby a hydrogen atom from some other part of the molecule attaches itself to the oxygen of the ketone group situated in the nucleus. If this is the case carvone will contain two double bonds, an assumption which is borne out by its behaviour. Carvone behaves like an $\alpha\beta$ unsaturated ketone, for with a mild reducing agent, such as zinc dust and alcohol, it takes up a molecule of hydrogen and passes into *dihydrocarvone*; with a stronger reducing agent, such as sodium and alcohol, the ketone group is also reduced and the secondary alcohol, *dihydrocarveol*, is formed, from which dihydrocarvone may be regenerated by oxidation. Both dihydrocarveol and dihydrocarvone are still unsaturated, for they combine with a molecule of hydrogen bromide, and further reduction converts them into *tetrahydrocarveol* (carvomenthol), which is a saturated secondary alcohol, yielding the ketone, *tetrahydrocarvone*, on oxidation. Having established the unsaturated nature of carvone, the next problem is to ascertain the positions of the two pairs of double bonds, for these have a special interest, seeing that they are probably common to both carvone and limonene. The problem has been approached by attempting to locate the position of each double bond separately, dihydrocarveol, which only contains one double bond, being first selected for the purpose.

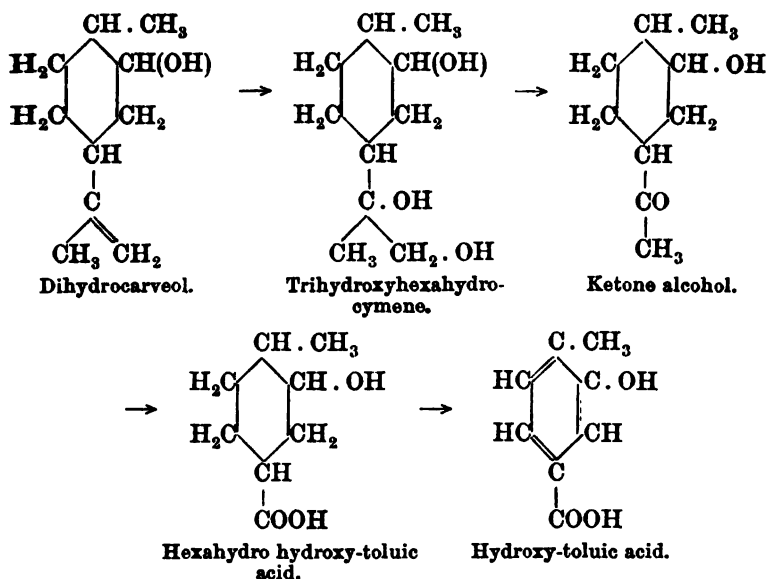
It is well known that unsaturated compounds are readily oxidised by permanganate solution, the first stage being the addition of two

¹ *Trans. Chem. Soc.*, 1877, 31, 554.

hydroxyl groups to the doubly linked carbon atoms, which is then followed by the rupture of the compound at the original double bond.

The action of permanganate solution upon dihydrocarveol has been carefully studied by Wallach,¹ and also by Tiemann and Semmler.² Two hydroxyls are first introduced and a trihydroxy-hexahydrocymene (menthanetriol) is obtained. Chromic acid converts the latter into a ketone alcohol of the formula $C_9H_{16}O_2$, which on oxidation with sodium hypobromite yields an acid, $C_7H_{12}(OH).COOH$, and this in turn, on being oxidised with bromine, gives *m*-hydroxy-*p*-toluic acid, $C_7H_6(OH).COOH$.

The simple explanation of these changes is based by Tiemann on the assumption of a double bond in the isopropyl side-chain.



If this view is correct the double bond in carvone and limonene is established. The position of the second double bond has been ascertained by reference to the structure of terpineol (m. p. 85°), which in turn is derived from that of terpin $C_{10}H_{18}(OH)_2$.

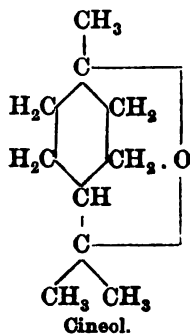
Terpin is the alcohol corresponding to dipentene dihydrobromide, for it can be obtained from the latter by the action of silver acetate and subsequent hydrolysis, or it may be converted by the reverse process into dipentene dihydrobromide with hydrogen bromide. *Terpin* is usually prepared by the action of strong nitric acid on an alcoholic solution of turpentine from which it crystallizes as the

¹ *Annalen*, 1898, 275, 110.

² *Ber.*, 1895, 28, 2141.

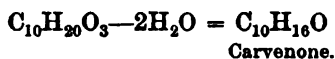
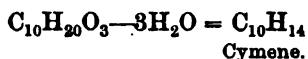
hydrate $C_{10}H_{18}(OH)_2 \cdot H_2O$, and the method is interesting as it affords a connecting link between the two terpenes, dipentene and pinene. Terpin exists in two stereoisomeric modifications as *cis* and *trans* terpin (p. 127). Although neither form of terpin has so far been found in nature, both are readily converted by dehydrating agents into two well-known natural products which accompany the terpenes in many of the essential oils, namely, cineol and terpineol (m. p. 35°), which are isomeric compounds of the formula $C_{10}H_{18}O$.

Cineol has no real connection with the problem under discussion, but by virtue of its interest as a natural product it merits a short description. As already stated, it is a common constituent of many essential oils and is specially abundant in eucalyptus, cajeput, and wormseed oil (*oleum cinac*). It is a liquid with a characteristic camphor-like smell and boils at 177°. As it possesses neither alcoholic nor ketonic properties and is closely related to terpin, it is regarded as an inner ether of that compound. Its structure therefore depends upon that of terpin, which is the subject of the present inquiry, and may be provisionally represented as follows:

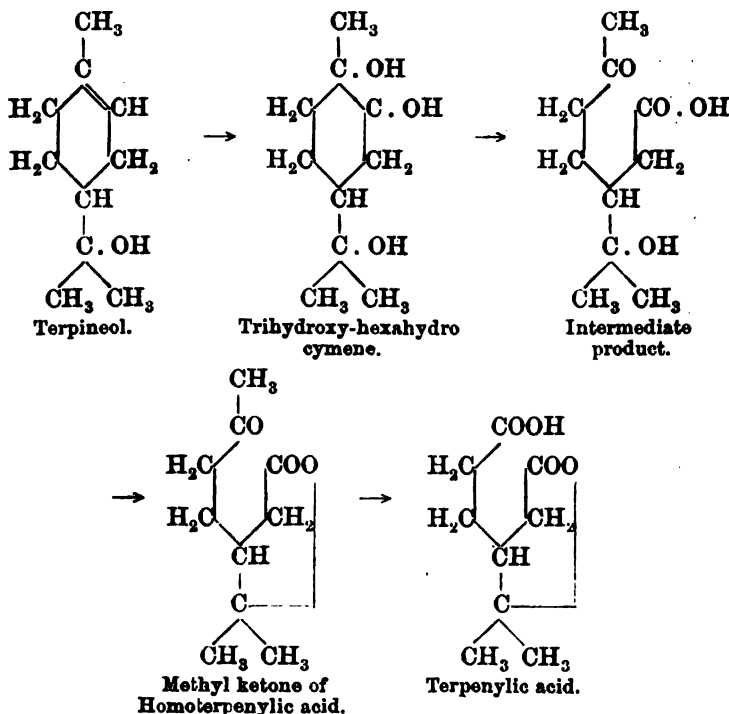


Terpineol (m. p. 35°) is one of a numerous class of unsaturated alcohols of the formula $C_{10}H_{17}OH$, known generally as terpineols or menthenols. It occurs in nature in active and inactive forms. The dextro form is found in lovage oil, cardamom, and marjoram oil; the laevo form in niaouli oil, and the inactive form in cajeput oil. It is conveniently prepared by shaking terpin hydrate with dilute sulphuric acid and separating the solid terpineol from the liquid products by freezing. It contains one tertiary alcohol group and one double bond, for it forms a phenylurethane with phenyl carbimide $C_{10}H_{17} \cdot O \cdot CONHC_6H_5$, and unites with one molecule of nitrosylchloride and of bromine. The hydroxyl group will probably occupy the same position as one of the terpin hydroxyls and therefore the same position as one of the halogen

atoms in dipentene dihydrobromide. As in the case of dihydrocarveol, the action of permanganate has led to very interesting results, for which we are indebted to Wallach.¹ The first product is a nearly quantitative yield of a trihydroxyhexahydrocymene (menthane triol), which is, however, not identical with that from dihydrocarveol (see p. 477), for on warming with dilute sulphuric acid it is decomposed into cymene and carvenone, while the other is not.



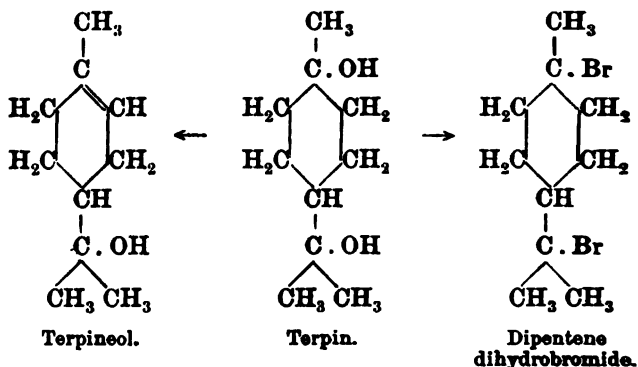
These changes will be discussed later (see p. 488). On further oxidation of the trihydroxy compound with chromic acid, it is converted successively into homoterpenylic acid and into terpenylic acid, the structure of which is known through Lawrence's synthesis.² Adopting Wagner's formula for terpineol, the results are explained by Wallach in a very simple fashion as follows:



¹ *Annalen*, 1898, 277, 110.

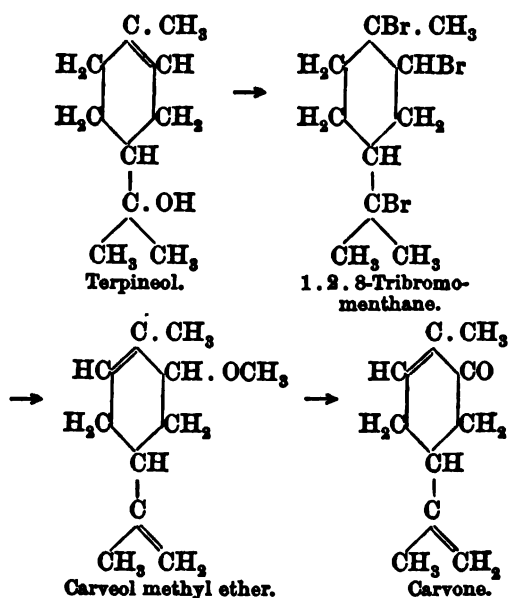
² *Trans. Chem. Soc.*, 1899, 75, 527.

It follows that as terpin is a bi-tertiary alcohol, its relation to terpineol on the one hand and dipentene dihydrobromide on the other must be represented as follows :

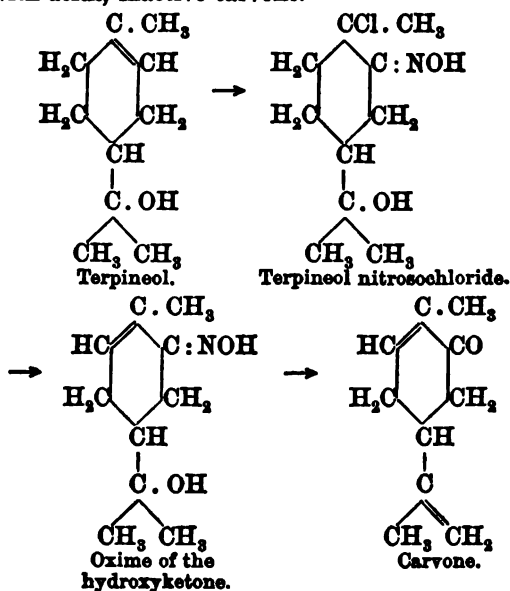


The existence of a *cis* and *trans* terpin (p. 478), and of corresponding dihydrobromides of dipentene, accords well with these formulae; but the structure of dipentene itself is still ambiguous, as the two molecules of hydrogen bromide may be removed from the hydrobromide in various ways. Now it has been shown that, as the oxime of carvone is identical with nitrosolimonene, the double bonds of carvone are probably identical in position with those of limonene. The position of one of these double bonds is fixed beyond question by the structure of dihydrocarveol; the other is probably present in terpineol. The final evidence must rest on the relation of terpinol to carvone, and this has been furnished by converting terpinol into carvone, and vice versa. Wallach¹ was the first to convert terpinol into carvone by the following rather lengthy process: terpinol forms a dibromide $\text{C}_{10}\text{H}_{17}\text{Br}_2 \cdot \text{OH}$, and this on standing with hydrobromic acid loses hydroxyl, which is replaced by bromine forming a tribromide (1.2.8-tribromomenthane) of the formula $\text{C}_{10}\text{H}_{17}\text{Br}_3$. Warmed with sodium methylate, carveol methyl ether is produced, $\text{C}_{10}\text{H}_{15} \cdot \text{OCH}_3$, two molecules of hydrogen bromide being removed and the third bromine atom replaced by methoxyl. This compound gives carvone oxidation :

¹ *Annalen*, 1894, 281, 140.

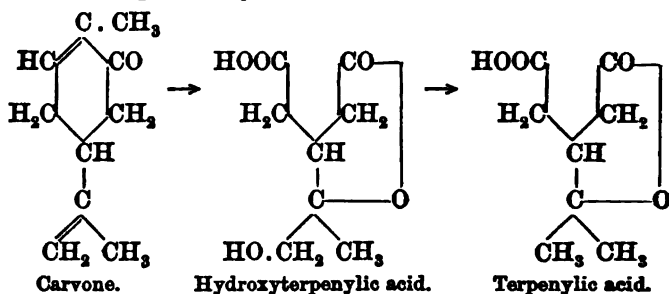


A simpler method, also devised by Wallach for effecting the same result, is to convert terpineol into the nitrosochloride and by removing hydrogen chloride to obtain the corresponding oxime, and finally, by boiling with acids, inactive carvone.¹

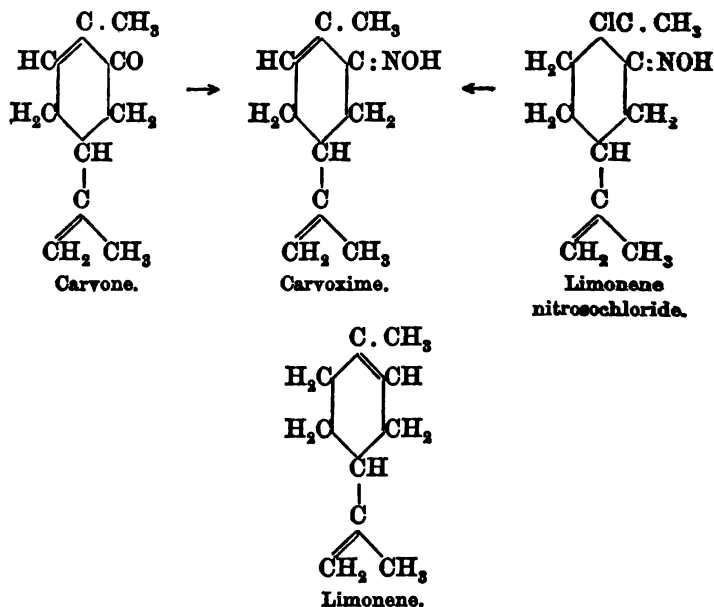


¹ *Annalen*, 1898, 277, 120.

On closer observation it will be seen that neither method makes it quite clear that the double bond lies in the nucleus, and not between the methyl group and the nucleus. Even the oxidation of carvone to terpenylic acid, which has also been effected,¹ does not remove such a possibility.



Assuming, however, the structure of carvone to be that given above, the formula for limonene and dipentene naturally follows.

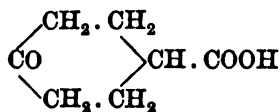


If any real doubt existed as to the correctness of the formula, it has now been to a great extent removed by the synthesis of terpin, terpineol, and dipentene, by W. H. Perkin, jun.²

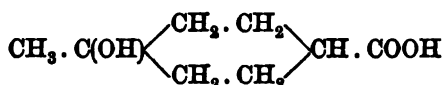
¹ Best, *Ber.*, 1894, 27, 1218; Wallach, *Ber.*, 1894, 27, 1495.

² *Trans. Chem. Soc.*, 1904, 85, 654.

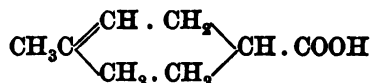
Perkin's synthesis is effected in the following manner. The starting-point is δ -ketohexahydrobenzoic acid.¹



Its ester reacts readily with magnesium methyl iodide, and the product on hydrolysis yields δ -hydroxyhexahydro-*p*-toluic acid.



This hydroxy acid dissolves readily in fuming hydrobromic acid, and the solution soon deposits crystals of δ -bromohexahydro-*p*-toluic acid, from which, on treatment with weak alkalis or pyridine, Δ^3 tetrahydro-*p*-toluic acid is obtained.



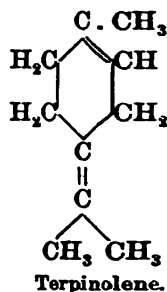
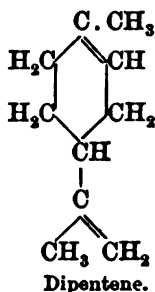
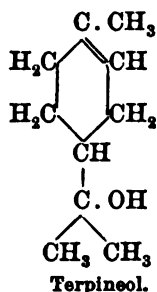
The ester of this acid, when acted on with magnesium methyl iodide, gives terpineol (see p. 491). The latter is transformed on the one hand into dipentene by the action of potassium hydrogen sulphate, and on the other into terpin hydrate by shaking with dilute sulphuric acid.

The structure of dipentene being thus satisfactorily settled, its formation from terpin, terpineol and cineol by dehydrating agents is readily understood without further explanation. But dipentene is not the only product of these reactions, for two other terpenes make their appearance at the same time, namely, terpinolene and terpinene.

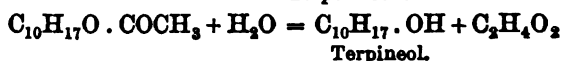
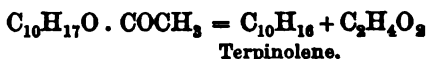
Terpinolene. Terpinolene is one of the artificial and inactive terpenes, which was found by Wallach among the products obtained by the inversion of pinene by means of alcoholic sulphuric acid. It can also be prepared, as already stated, from terpin, terpineol, or cineol, by boiling with dilute sulphuric or phosphoric acid. Terpinene is usually found to accompany terpinolene, and, where sulphuric acid is used, cymene is also produced. The best method for obtaining it is by the action of oxalic acid on terpineol (*m.p.* 85°). Since the elements of water may be eliminated from the two adjacent

¹ *Trans. Chem. Soc.*, 1904, 85, 188, 416.

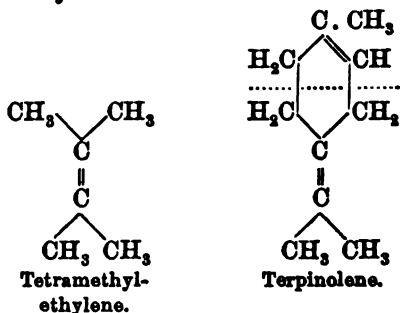
carbon atoms of terpineol in two ways, one of which yields dipentene the other derivative will probably represent terpinolene.



This line of argument would not in itself carry much weight a similar reaction yielding terpinene, had not independent evidence been forthcoming in support of the above constitution. Terpinolene has been obtained by Baeyer¹ from dipentene tribromide, $C_{10}H_{17}Br_3$, the latter being obtained by brominating dipentene dihydrobromide. If the tribromide is treated with zinc dust and acetic acid, two atoms of bromine are removed and the third replaced by hydroxy-acetyl, forming terpineol acetate, $C_{10}H_{17}O \cdot COCH_3$, and this on distillation with quinoline yields acetic acid and terpinolene, or, on hydrolysis, gives a new terpineol (*m. p.* 70°).



The evidence upon which the structure of terpineol acetate rests is the formation of a blue crystalline nitrosochloride, which is indistinguishable in appearance from the nitrosochloride of tetramethylethylene prepared by Thiele.²

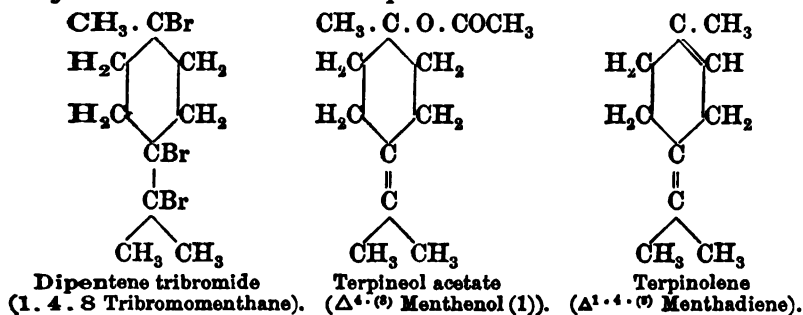


Baeyer concluded that both compounds possess a similar structure

¹ Ber., 1894, 27, 443, 815.

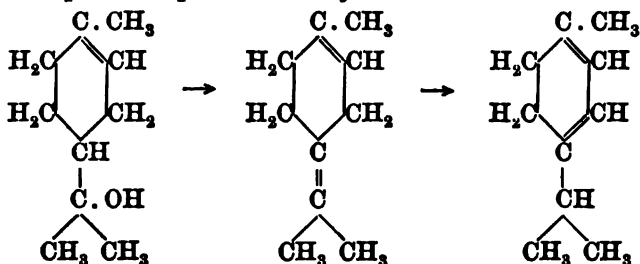
² Ber., 1894, 27, 455.

The various steps in the preparation of terpinolene from dipentene dibromide will then be expressed as follows :



Terpinene. Terpinene is formed, as already stated, from terpin hydrate, terpineol and cineol, and substances such as pinene and dipentene, which are easily converted into terpin hydrate by means of sulphuric acid ; but it is most readily obtained by shaking turpentine oil (pinene) with small successive quantities of strong sulphuric acid. So far its occurrence in nature seems very restricted, for it has been found in few of the essential oils. Its presence in cardamom oil was first noticed by Weber, who identified it by means of the crystalline nitrosite, $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_3$, which it gives with nitrous acid, and which is characteristic both of terpinene and phellandrene. Few other of its additive compounds are crystalline, and no definite products have been obtained by oxidation.

For the present, therefore, its structure remains undetermined, but it is probable that the simultaneous formation of terpinolene from terpineol may indicate a shifting of the double bond of terpinolene from the side-chain to the nucleus, and such a structure would at least explain its optical inactivity.

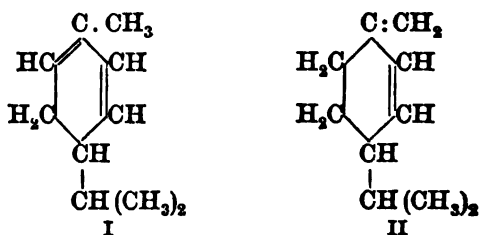


Phellandrene. Phellandrene, like terpinene, forms a crystalline nitrosite, and in this form it was first isolated by Cahours¹ in 1842. It has since been found in two active modifications, the *d*-compound

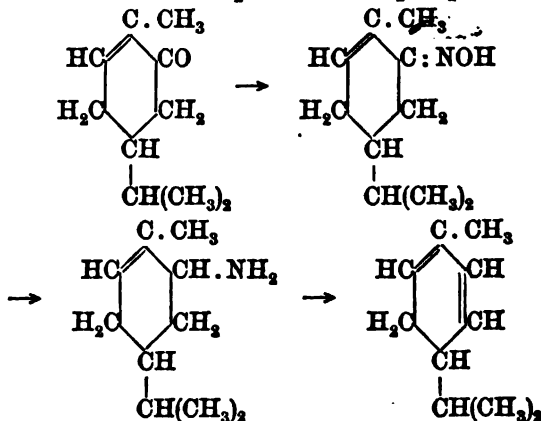
¹ *Annalen*, 1842, 41, 74.

occurring in bitter- and water-fennel oil (*Phellandrium aquaticum* and elemi oil, and the *l*-compound in Australian eucalyptus oil and pine-needle oil. It is very sensitive to acids, and with alcoholic sulphuric acid is converted into terpinene.

In the year 1904 Wallach¹ published a very complete investigation on the nature of phellandrene, and pointed out that in addition to ordinary or α -phellandrene a second or β -phellandrene is present in water-fennel oil. The first was shown to have the structure of $\Delta^{3,6}$ dihydrocymene (I) by the conversion of nitrophellandrene into active menthenone (carvotanacetone), whilst β -phellandrene which formed the subject of a subsequent investigation by Wallach² was shown to possess the formula II:



Harries and Johnson³ confirmed the formula given to α -phellandrene by the reverse process to that employed by Wallach, namely, by converting *d*-menthenone into phellandrene as follows: menthenone is first treated with phosphorus pentachloride, and the resulting chloride converted into chlorophellandrene by boiling with quinoline. The chlorophellandrene, on reduction with zinc dust in methyl alcohol, yields α -phellandrene. Another and better method is to reduce menthenoneoxime to Δ^6 menthenamine, and to distil the product under diminished pressure with phosphoric acid.

¹ *Annalen*, 1904, 336, 9.² *Annalen*, 1905, 340, 1.³ *Ber.*, 1905, 38, 1832

Carvestrene and Sylvestrene. The only menthadienes of the meta-series are carvestrene, the inactive, and sylvestrene, the active form.

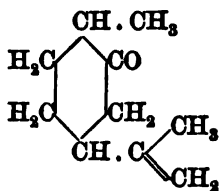
Sylvestrene was first discovered in 1877 by Atterberg in Swedish turpentine (from *Pinus sylvestris*), which is still the principal source of the compound, although it has since been found in dwarf pine oil (from *Pinus montana*) and pine tar oil. It is purified by separating it from the crystalline dihydrochloride by boiling with aniline, and is a curiously stable substance, retaining its optical activity (it is dextro-rotatory) at a temperature of 250°, and undergoing little change by the action of alcoholic sulphuric acid. Both carvestrene and sylvestrene give a characteristic deep blue colour on the addition of a drop of strong sulphuric acid to the terpene dissolved in acetic anhydride, a property which is not shared by any other terpene.

The conversion of sylvestrene into *m*-cymene (see p. 472) and its evident relation to carvestrene point to a common structure for both compounds. This structure will now be considered in the case of carvestrene.

Carvestrene is an artificial compound, which was obtained by Baeyer¹ by distilling vestrylamine hydrochloride.

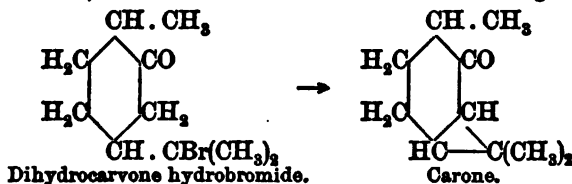


The formation of this base involves a series of complex changes which take us back to dihydrocarvone (p. 476), which, it may be remembered, is the first reduction product of carvone.



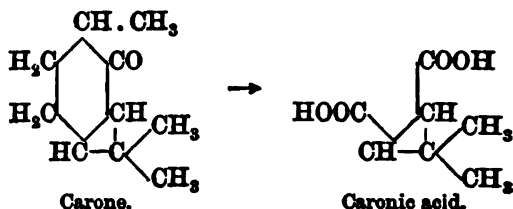
Dihydrocarvone.

This substance readily forms a hydrobromide from which methyl alcoholic potash removes a molecule of hydrogen bromide; but with the production of an entirely new compound, namely, a saturated bicyclic ketone, to which the name of *carone* has been given.

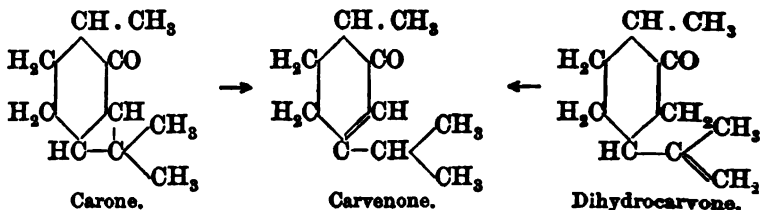


¹ Ber., 1894, 27, 1915, 3485; 1896, 29, 2796.

Carone has a smell of camphor and peppermint, and is optically active in the sense corresponding to the two carvones from which it may be prepared. The structure of carone is not a mere surmise but depends on the formation of caronic acid by oxidation; for the same acid has been obtained synthetically by Perkin, jun., and Thorpe,¹ who have identified it as dimethylcyclopropane dicarboxylic acid.

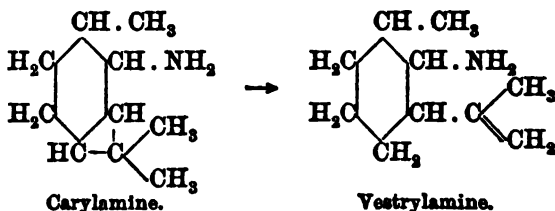


The existence of such an acid clearly points to a trimethylene ring in carone. An additional proof of its structure is its conversion on heating into carvenone. Carvenone is an unsaturated ketone which is also obtained by the isomeric change of dihydrocarvone on boiling with acids (p. 178).

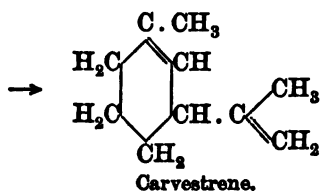


Having settled the structure of carone, the subsequent changes are readily explained.

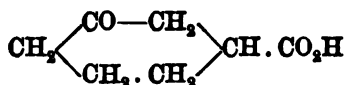
Carone forms an oxime which is reduced to carylamine. If the alcoholic solution of carylamine is saturated with hydrogen chloride gas, the unsaturated base, *vestrylamine*, is formed, from the hydrochloride of which carvestrene is generated.



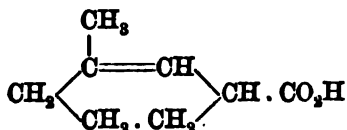
¹ *Trans. Chem. Soc.*, 1899, 75, 48.



Carvestrene has been recently synthesized by Perkin, jun., and Tattersall¹ as follows: *m*-hydroxybenzoic acid is first reduced to the hexahydro derivative and subsequently oxidized to cyclohexanone-8-carboxylic acid.

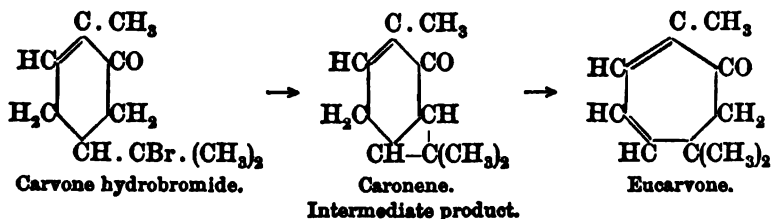


Methyl and hydroxyl are then introduced by Grignard's method in place of the ketonic oxygen, hydroxyl is replaced by bromine, and hydrogen bromide is then removed.



The tetrahydro-*m*-toluic acid thus formed is converted into the ester, and the subsequent stages are the same as those described under the synthesis of *p*-menthadiene from tetrahydro-*p*-toluic ester on p. 491.

The action of methyl alcoholic potash on carvone hydrobromide gives rise to the unsaturated ketone, *eucarvone*, $\text{C}_{10}\text{H}_{14}\text{O}$.² The fact is referred to as it illustrates in a graphic manner the remarkable reactivity of these cyclic structures, which reaches perhaps its culminating point in the case of camphor. Eucarvone is probably a seven-ring complex, in the formation of which caronene probably plays the part of an intermediate product.

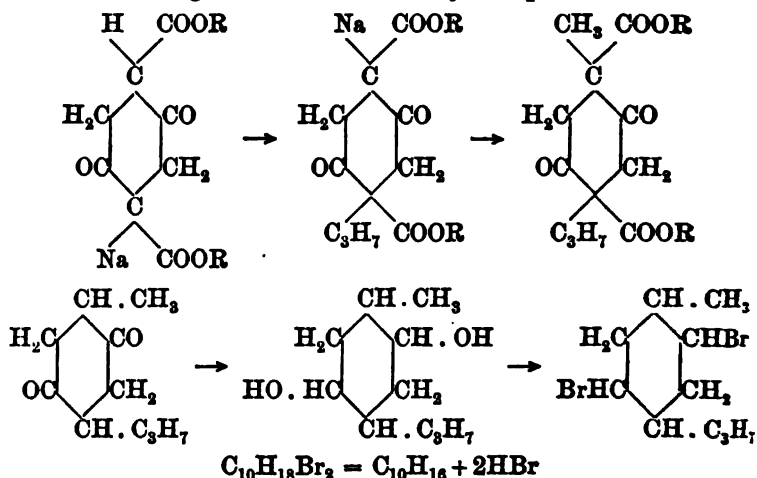


¹ *Trans. Chem. Soc.*, 1907, 91, 480.

² *Baeyer, Ber.*, 1894, 27, 811; 1896, 29, 3; Wallach and Köhler, *Annalen*, 1905, 339, 94.

The existence of a seven-ring system is based upon the oxidation of tetrahydroeucarvone to β -dimethyladipic acid.

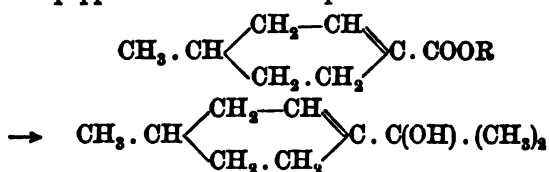
Synthetic Terpenes. We will conclude our account of the mono-cyclic terpenes by a short reference to the various attempts which have been made to obtain these compounds synthetically. It is true that several artificial terpenes have been described, but some of them can scarcely be considered as products of constructive synthesis, seeing that the materials have been drawn from natural sources. The first complete and successful synthesis was accomplished by Baeyer¹ as follows: succino succinic ester was treated with one equivalent of sodium ethoxide and one equivalent of isopropyl iodide, whereby a mono-isopropyl derivative was obtained. The process was repeated, using, however, one equivalent of methyl iodide. This yields a methyl isopropyl derivative, which is then heated with sulphuric acid. Hydrolysis occurs, and at the same time carbon dioxide is evolved with the formation of methyl isopropyl diketocyclohexane. The ketone was reduced to the alcohol, the hydroxyls replaced by bromine by treatment with strong hydrobromic acid, and, finally, the product heated with quinoline, which removes two molecules of hydrogen bromide. In this way a *p*-menthadiene was produced, which, though closely resembling, was not identical with terpinene. The various changes described above may be represented as follows:



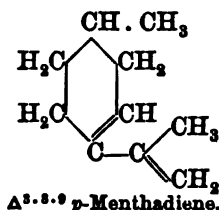
The structure of the terpene in question will obviously depend upon the manner in which the two molecules of hydrogen bromide are detached.

¹ Ber., 1893, 26, 232.

The successful syntheses of dipentene and carvestrene by Perkin, jun., have already been referred to. The same author and his collaborators,¹ by a slight variation of the method, have succeeded in preparing artificially ortho-, meta- and para-terpenes (menthadienes), terpeneols (menthenols), and the allied menthanols and menthanes, of which the following single illustration must suffice. The starting-point is the ester of tetrahydrotoluic acid, which is obtained by removing hydrogen bromide from the corresponding bromo-hexahydrotoluic acid. Ethyl Δ^3 -tetrahydro-*p*-toluate reacts with an ethereal solution of magnesium methyl iodide, yielding Δ^3 *p*-menthenol, which possesses the peppermint odour of terpeneol.

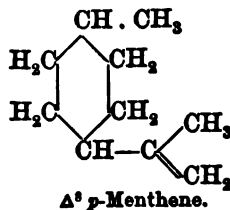
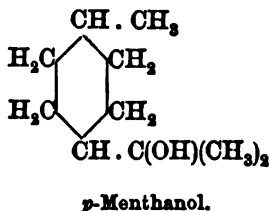


On digesting the latter with potassium hydrogen sulphate, water is removed and $\Delta^{3,8,9}$ *p*-menthadiene is formed.



This new terpene differs in many important characters from dipentene, more especially in the fact that it combines with only one molecule instead of two molecules of bromine, hydrogen chloride and bromide. This is ascribed to the presence of the conjugated system of double linkings C:C:C:C, in which bromine is known to unite only with the end carbon atoms forming the group CBr.C:C.CBr (see p. 452).

By a similar series of reactions to the above, using ethyl hexahydro-*p*-toluate, *p*-menthanol and Δ^8 *p*-menthene were prepared.

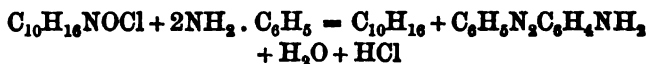


¹ *Trans. Chem. Soc.*, 1905, 87, 689, 661, 1066, 1088.

Finally, from *p*-menthene, *p*-menthane (hexahydrocymene) was obtained by reducing the additive compound of *p*-menthene and hydrogen bromide, $C_{10}H_{18}HBr$, with zinc dust and acetic acid. Similar reactions have been carried out with the esters of hexa- and tetra-hydrobenzoic acid, hexa- and tetra-hydro-*o*-toluic acid, and hexa- and tetra-hydro-*m*-toluic acid.

THE BI-CYCLIC TERPENES

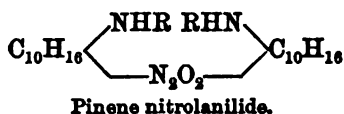
Pinene. Pinene is the most widely distributed of all the terpenes. It is a common constituent of most essential oils, and is specially abundant in the resinous exudations of different species of *pinus*, from which it is obtained by distillation in the form of turpentine oil. Two optically active modifications are known, the *d*-compound, sometimes distinguished by the name *australene*, being found in American turpentine (from *Pinus palustris* or *australis*), and also in German, Russian, and Swedish turpentine (from *Pinus sylvestris*) and in many essential oils, and the *l*-compound or *terebenthene* in French turpentine (from *Pinus pinaster*), English pine needle oil, hemlock oil, &c. It is still doubtful whether the two are strictly enantiomorphous. Pinene from pine is obtained by first fractionating turpentine oil and then converting it into the crystalline nitrosochloride, from which, by boiling with aniline in alcoholic solution, the pure but inactive compound is regenerated. In this reaction aminoazobenzene is also formed.



Pinene contains one double bond; for, as just stated, it forms a compound with one molecule of nitrosyl chloride, to which Baeyer assigns the double molecular formula:

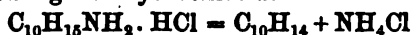


This compound forms a series of *nitrolamides* by the exchange of chlorine for primary basic groups having the general formula:

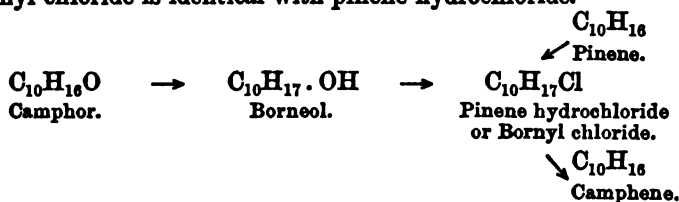


Sodium alcoholate removes hydrogen chloride from the nitrosochloride, forming *nitrosopinene*, $C_{10}H_{16}NO$, which can be reduced to

pinylamine, $C_{10}H_{16} \cdot NH_2$. The latter is readily converted into *p*-cymene by distilling the hydrochloride.



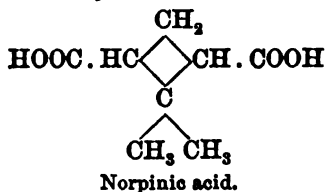
In addition to the nitrosochloride, pinene forms crystalline additive compounds with one molecule of dry hydrogen chloride and bromide, $C_{10}H_{16}HCl$ and $C_{10}H_{16}HBr$, from which the original product cannot be regenerated; for on removing the halide acid with quinoline or sodium acetate a new terpene, namely *camphene*, is produced. Now camphene is closely related to *camphor*, for camphor $C_{10}H_{16}O$ on reduction forms *borneol* $C_{10}H_{17}OH$, which is a secondary alcohol giving with phosphorus chloride *bornyl chloride*, and bornyl chloride is identical with pinene hydrochloride.



When it is remembered that pinene is converted by moist hydrogen chloride into dipentene dihydrochloride, and by alcoholic sulphuric acid and other reagents into such varied products as terpin hydrate, terpineol, cineol, dipentene, terpinolene and terpinene, it is easy to realize that the structure of pinene is a pivot upon which that of nearly the whole terpene and camphor family turns. A correct interpretation of its structure is therefore of the highest importance, but its remarkable reactivity rather enhances than diminishes the difficulty of the problem. The successful solution of the problem is mainly due to the combined labours of Baeyer, Tiemann, and Wagner. As in other cases the most valuable information has been gathered from the behaviour of pinene on oxidation. Let us follow the steps in this process of dismemberment. By the action of free oxygen and water on pinene, Sobrero obtained the crystalline *pinol hydrate* or *sobrero*, $C_{10}H_{16}(OH)_2$, which on warming with dilute hydrochloric acid is converted into *pinol*, $C_{10}H_{16}O$. Both *sobrero* and *pinol* are neutral compounds whose constitution will be explained presently. By means of permanganate solution, Baeyer¹ obtained a much more complete series of oxidation products. He found among the first products two acids, namely *α -pinonic acid*, $C_{10}H_{16}O_3$, and *pinoyl formic acid*, $C_{10}H_{14}O_5$. The first is a ketonic monobasic acid, and the second a ketonic dibasic acid. As both acids yield on further oxidation the same dibasic *pinic acid*,

¹ Ber., 1896, 29, 1907.

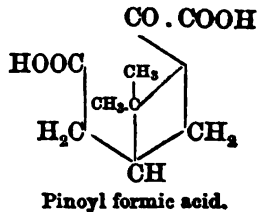
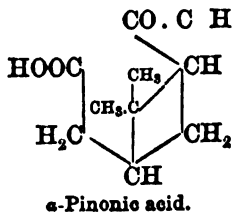
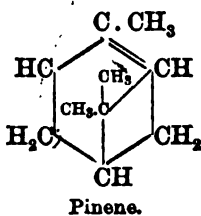
$C_7H_{12}(COOH)_2$, Baeyer¹ concluded that they contain respectively a methyl ketone— $CO \cdot CH_3$, and an α -ketonic acid— $CO \cdot COOH$ group. Pinic acid is very stable; but by first converting it into hydroxypinic acid (by bromination and subsequent hydrolysis), it may be further oxidised to the lower homologue *norpinic acid* $C_6H_{10}(COOH)_2$, a dibasic acid which resists further oxidation. The structure of norpinic acid, which is the key to the problem, is regarded by Baeyer as a cyclobutane derivative.



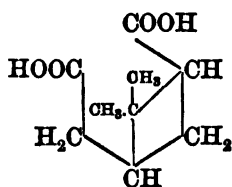
Like carone which gives caronic acid, and therefore contains a cyclopropane nucleus, so pinene must contain a bridged ring, of which one part consists of four carbon atoms.

Both α -pinonic and pinoyl formic acids are very unstable in acid solution, and like pinene itself are readily transformed by hot dilute sulphuric acid into isomeric compounds, a change which Baeyer ascribes to the rupture of the cyclobutane ring. Pinonic acid gives the methyl ketone of homoterpenylic acid, which Wallach had previously obtained by the oxidation of terpineol (p. 478), whereas pinoyl formic acid is converted into homoterpenyl formic acid, which in turn can be oxidised to homoterpenylic and terpenylic acid of known constitution.

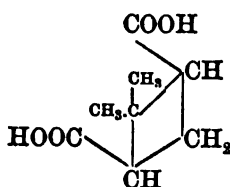
Adopting Wagner's formula for pinene, Baeyer explains the various steps as follows:



¹ Ber., 1896, 29, 1907.

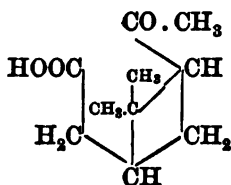
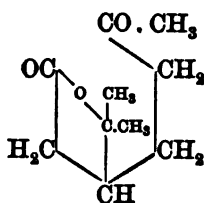
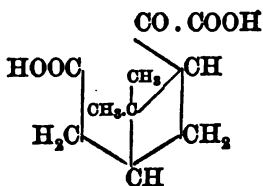


Pinic acid.

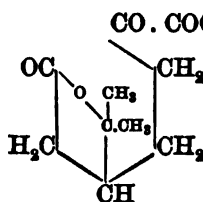


Norpinic acid.

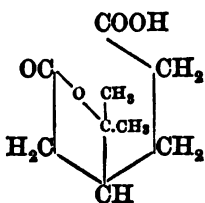
α -Pinonic acid is therefore produced by the rupture of the double bond in pinene. The decomposition of α -pinonic and pinoyl formic acid by sulphuric acid is represented as follows :

 α -Pinonic acid,Methyl ketone of
Homoterpenylic lactone.

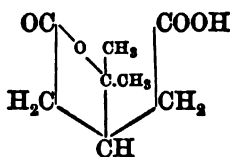
Pinoyl formic acid.



Homoterpenyl formic acid.



Homoterpenylic acid,



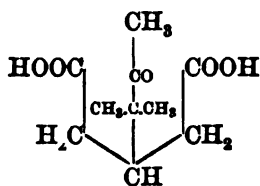
Terpenylic acid.

This view of the structure of pinene, which fits in so neatly with the facts described above, is opposed to the observations of Tiemann and Semmler.¹ Tiemann and Semmler, like Baeyer, submitted pinene to the oxidising action of permanganate, and obtained a saturated ketonic acid, pinonic acid, which, on further oxidation

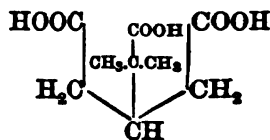
¹ Ber., 1896, 29, 529, 8027.

with chromic acid mixture, gave a dibasic ketonic acid, isoketocamphoric acid, $C_{10}H_{16}O_6$, isocamphoronic acid, $C_9H_{14}O_6$, and terebinthic acid, $C_7H_{10}O_4$, whilst alkaline permanganate converted it into dimethyltricarballic acid.

Now the constitution of isoketocamphoric acid is known, partly from its chemical properties but mainly from its relation to isocamphoronic acid, which it yields on oxidation,¹ and whose structure has been established beyond question by its synthesis by Perkin² (p. 289). The two compounds must be represented as follows:

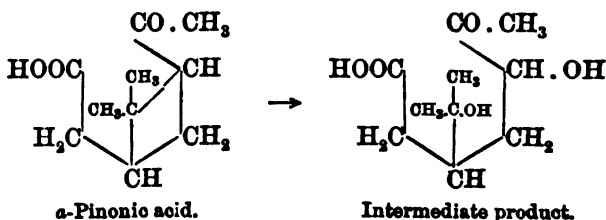


Isoketocamphoric acid.

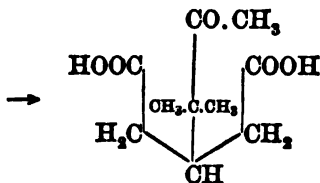


Isocamphoronic acid.

It is impossible by any device to rupture the bonds in Wagner's pinene formula so as to yield either of these acids, and the only alternative is to suppose that an internal rearrangement of the molecule of α -pinonic acid occurs during oxidation after the following fashion:

 α -Pinonic acid.

Intermediate product.



Isoketocamphoric acid.

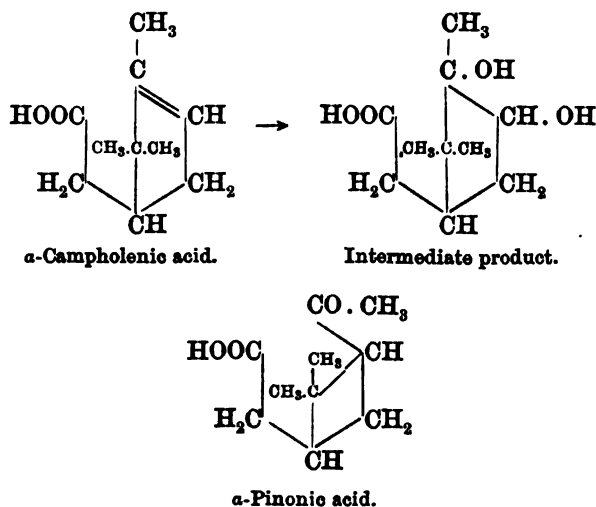
Another difficulty encountered by Wagner's formula is the formation of pinonic from α -campholenic acid. The latter acid is obtained

¹ *Trans. Chem. Soc.*, 1899, 75, 900.

² Perkin, jun., *Proc. Chem. Soc.*, 1900, 16, 214.

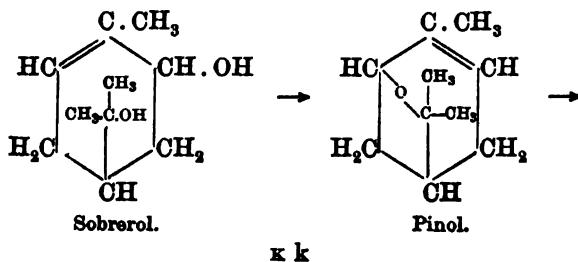
from camphor, and its structure, which is discussed on p. 522, presents no ambiguity.

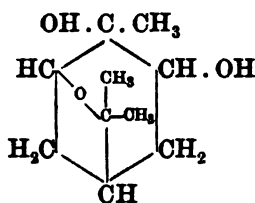
The explanation which is here put forward is based upon the pinacone-pinacolone change (p. 209).



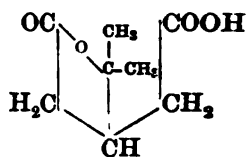
Having now laid the foundation upon which the formula for pinene rests, and attempted to adjust its structure to that of isocamphoronic and α -campholenic acid, let us examine for a moment its relation to the first products of oxidation, namely, sobrerol and pinol, and finally to the allied terpene, dipentene.

The formation of sobrerol is explained by the rupture of the cyclobutane ring, that of pinol by the loss of water from sobrerol and formation of an inner ether. As both compounds are oxidized by permanganate, one to pinolglycol, $C_{10}H_{16}(OH)_2O$, and the other to sobrerithritol, $C_{10}H_{16}(OH)_4$, they must still possess a double bond. Furthermore, pinolglycol gives terpenylic acid on oxidation. These results are expressed by the following formulae:



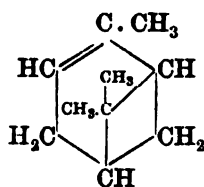


Pinolglycol.

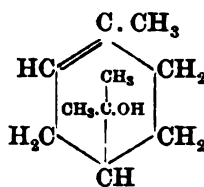


Terpenylic acid.

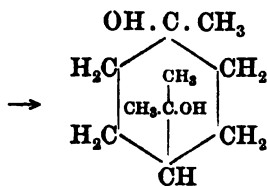
In the formation of dipentene, pinene passes through the intermediate stages of terpineol and terpin, and here again the inner ring is broken.



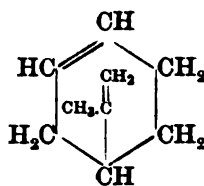
Pinene.



Terpineol.



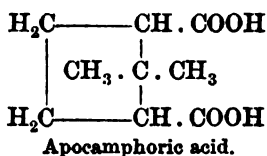
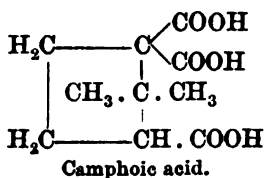
Terpin.



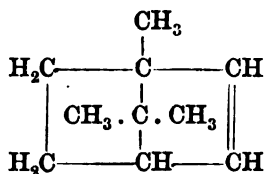
Dipentene.

Camphene. Camphene is a solid terpene. It is dextro-rotatory in ginger and spike oil, and laevo-rotatory in citronella and valerian oil, and in French and American turpentine. Berthelot obtained the same two active forms from *d*- and *l*-pinene by the action of dry hydrogen chloride, which converts them into the corresponding *d*- and *l*-bornyl chlorides (p. 499). It is also obtained from borneol and the isomeric isoborneol (p. 500) by the action of dehydrating agents. Its mode of preparation would naturally suggest that camphene contained a double bond, and this is supported by the following evidence: the molecular refraction constant observed by Brühl, the formation of a hydrochlorocamphene, $C_{10}H_{17}Cl$, with hydrogen chloride gas, of a dibromide $C_{10}H_{16}Br_2$, with bromine, and of a glycol, $C_{10}H_{16}(OH)_2$, by the action of dilute permanganate. Oxidised with nitric acid it yields camphoic acid,

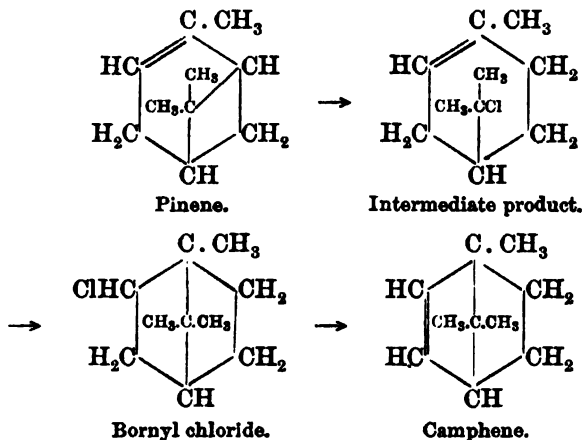
which, on heating, loses carbon dioxide and forms apocamphoric acid, which has been synthesized by Komppa¹ (p. 267).



It would appear from this array of simple facts that the structure of camphene would offer no difficulty, and indeed for a long time the following formula was accepted without question :



It explains primarily its relation to camphor and borneol (see p. 498), and is consistent with the facts enumerated above, including its formation from pinene, which is expressed as follows:



Nevertheless, this view is contested by Wagner and Semmler, and is based on the nature of the halogen compounds from which camphene is prepared.

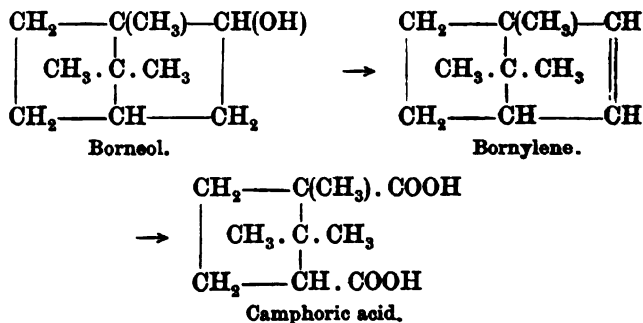
In the first place, the additive compounds of pinene and camphene with hydrogen chloride are not identical, for the pinene compound is much the more stable. Pinene hydrochloride resists the action of

¹ Ber., 1901, 34, 2472.

boiling water to a great extent, whilst the camphene compound almost completely loses hydrogen chloride by this treatment.

Corresponding to these two hydrochlorides are two borneols, known as borneol and isoborneol, both of which are obtained simultaneously by the reduction of camphor with sodium in alcoholic solution. By the action of phosphorus pentachloride on isoborneol, or hydrogen chloride on its alcoholic solution, camphene hydrochloride is produced. Moreover, camphene combines with organic acids in presence of sulphuric acid to form esters of isoborneol. It seems clear, therefore, that camphene and isoborneol are structurally related. Wagner and Brykner¹ have now shown that, when phosphorus pentachloride reacts with borneol, a mixture of bornyl and isobornyl chloride is produced, but mainly the latter, which proves to be a secondary product of the action of hydrogen chloride on the camphene formed by the dehydration of borneol. If in place of phosphorus pentachloride, dry hydrogen iodide is allowed to react with borneol, bornyl iodide is formed, from which alcoholic potash liberates a new terpene, called *bornylene*. As bornyl iodide is identical with pinene hydriodide, there is little doubt that pinene hydrochloride is the true halogen ester of borneol.

As both borneol and isoborneol give camphor on oxidation, and until recently were thought to yield camphene by dehydration, the differences between them were regarded as of a stereochemical nature. With the discovery of bornylene and the great divergence which is now recognized in the properties not only of bornylene and camphene but of borneol and isoborneol, this view has undergone a change, and they are looked upon as structurally distinct. Bornylene has received the formula originally attached to camphene, and best indicates its relation to borneol and to camphoric acid, which it readily yields on oxidation (p. 509).

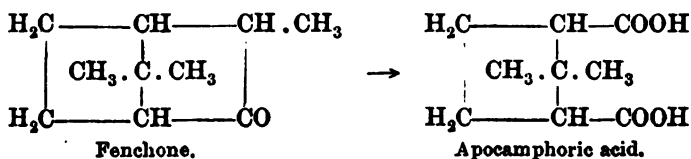


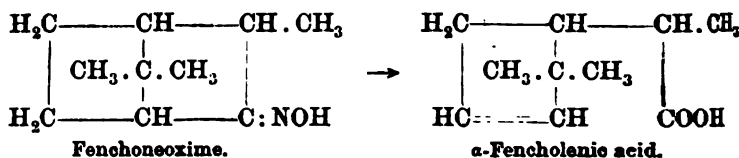
¹ Ber., 1899, 32, 2320; 1900, 33, 2121.

The structure of camphene is still doubtful. By carefully regulated oxidation, Wagner obtained a camphene glycol, $C_{10}H_{16}(OH)_2$, which is, however, quite distinct from camphor glycol. From camphene glycol a series of oxidation products have been prepared, among which a dibasic acid, camphenecamphoric acid, $C_{10}H_{16}O_4$, a hydroxy acid, camphenylic acid, $C_{10}H_{16}O_3$, and a ketone, camphenilone, $C_9H_{14}O$, have been isolated and studied.

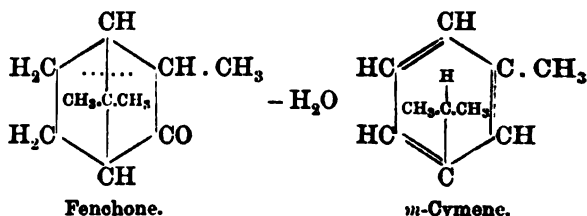
In another direction the action of chromylchloride has produced an aldehyde camphenilan aldehyde, $C_9H_{16}CHO$, from which camphenilanic acid has been prepared. This acid has been converted successively into a bromo and a hydroxy acid, the latter being identical with camphenilone. In the present state of the camphene problem it seems useless to multiply the names and formulae of its derivatives, and the subject must be left until further research has thrown new light upon it.

Fenchene. Two active fenchenes are prepared from corresponding fenchones much in the same way that bornylene or camphene are prepared from camphor. It is therefore necessary to preface a description of their preparation with some account of fenchone. Fenchone, $C_{10}H_{16}O$, was discovered by Wallach in 1890. It is dextrogyrate in fennel oil (*foeniculum vulgare*) and laevogyrate in thuja oil, in which it occurs with *thujone*, an isomeric ketone. Fenchone has similar properties to camphor (p. 510), but is a liquid. It is a ketone, and forms an oxime, but contains no CH_2CO group, since it yields no hydroxymethylene compound. On reduction it gives a secondary alcohol, *fenchyl alcohol*, $C_{10}H_{18}O$, from which various terpenes of the formula $C_{10}H_{16}$, the fenchenes, can be obtained by the aid of dehydrating agents. Oxidising agents convert fenchene into apocamphoric acid (p. 499), whilst fenchone gives isocamphoronic acid (p. 496). Fenchoneoxime, like camphoroxime, loses water on heating with acids, and gives unsaturated fencholenic nitriles which, on hydrolysis, are converted into α - and β -fencholenic acids. These facts have found expression in the following formulae for fenchone and its derivatives:



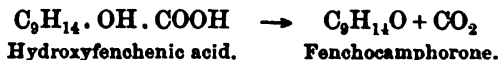


Its relation to *m*-cymene is readily expressed by means of the above formula by breaking one bond of the bridge at the dotted line and removing a molecule of water.

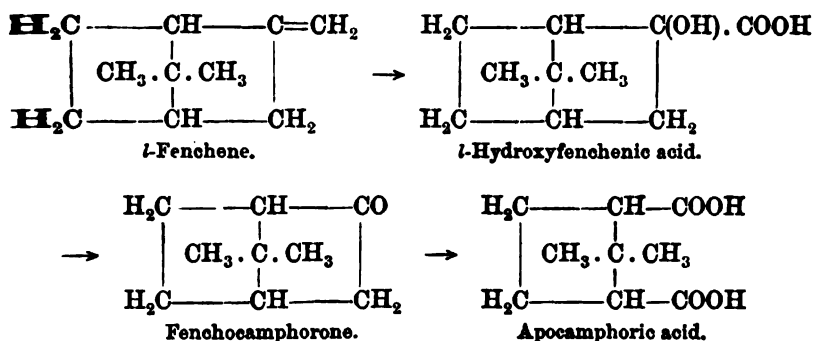


In addition to the action of dehydrating agents on the fenchyl alcohols, the fenchenes may be prepared by removing hydrogen chloride from the fenchyl chlorides, which are in turn formed from the alcohols by the action of phosphorus chloride. In this way a variety of fenchenes are obtained according to the method of preparation, of which only the structure of one, namely, *l*-fenchene from *d*-fenchone, is accurately known. In its preparation *d*-fenchone is reduced to fenchyl alcohol, which is laevo-rotatory. If carefully cooled when phosphorus chloride is added, a strongly laevo-rotatory fenchyl chloride is formed, from which *l*-fenchene is obtained by removing hydrogen chloride with aniline. It is a curious fact that if the fenchyl alcohol is not cooled during the action of the phosphorus compound, the product is dextro-rotatory.

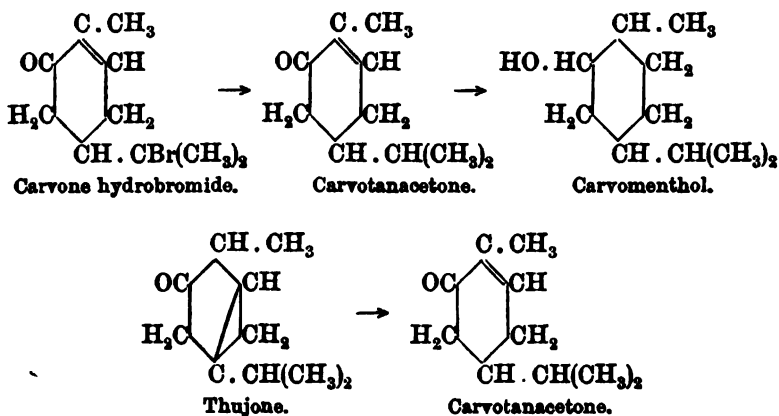
The constitution of *l*-fenchene has been arrived at by Wallach by a study of its oxidation products. It yields a hydroxyfenchenic acid, $\text{C}_{10}\text{H}_{16}\text{O}_3$, which, like α -hydroxy acids, is converted by means of lead peroxide and sulphuric acid into a ketone, fenchocamphorone, with elimination of carbon dioxide.



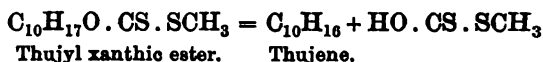
Fenchocamphorone yields, on the one hand, an oxime which readily loses water and passes into fenchocamphonitrile, $\text{C}_9\text{H}_{13}\text{CN}$, and on the other passes by oxidation into apocamphoric acid. These changes are represented by the following formulae :



Thujene. Thujene, like fenchene, is obtained from the corresponding ketone, *thujone* or *tanacetone*, which accompanies *l*-fenchone in thuja oil, and is also found in the oils of tansy, wormwood, and sage. Thujone is separated as the bisulphite compound and is dextrogyrate. As the constitution of thujone is bound up with that of thujene, we will consider the properties of the former first. Thujone forms a semicarbazone and an oxime, which gives *thujylamine*, $\text{C}_{10}\text{H}_{17}\text{NH}_2$, on reduction. It is saturated, i.e. it yields no additive products, and therefore presumably is a bi-cyclic ketone of the nature of carone. Its relationship to carone is further demonstrated by the action of heat, which converts it into the isomeric carvotanacetone in the same manner that carone yields carvenone (p. 488). Now the structure of carvotanacetone is known and is derived partly from its formation from carvone hydrobromide by reduction and partly by its conversion into carvomenthol, the isomer of menthol. These facts are expressed by the following structural formulae:



Wallach found that thujone undergoes a further isomeric change on boiling with sulphuric acid, yielding an unsaturated ketone, *isothujone*, which, according to Semmler, contains a cyclopentane nucleus; but the consideration of this compound need not detain us. Thujene can be prepared from thujone by means of the xanthic ester method elaborated by Tschugaeff, and which seems capable of a very wide application (p. 474). Thujyl alcohol, which is obtained from thujone by reduction, is converted into the xanthic methyl ester by treating the sodium compound of the alcohol with methyl iodide and carbon bisulphide. It is then decomposed by dry distillation and gives the terpene:



We have not exhausted the subject of the terpenes, nor even enumerated all the known members. We have been content to give a sufficiently broad *résumé* of this branch of organic chemistry to enable the reader to realize the nature and remarkable reactivity of these substances.

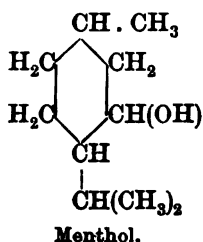
THE CAMPHORS

It has already been stated that many oxygen compounds closely allied to the terpenes in chemical structure are found associated with them in plants. Cineol and terpineol have already been described, and here and there a reference has been made to substances having the formula $\text{C}_{10}\text{H}_{16}\text{O}$, and possessing the properties of ketones. Some of these, like the artificial products dihydrocarvone or carvenone, are unsaturated and have a monocyclic structure, others again, like natural fenchone and thujone, or carone which is prepared from carvone, are saturated and contain a bi-cyclic nucleus. The ketones are therefore divisible into two groups like the terpenes. In addition to the above are two important members of the camphor group, namely, *pulegone*, which belongs to the monocyclic division, and *camphor*, which must be included in the bi-cyclic division.

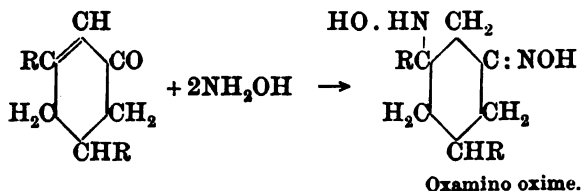
Pulegone. Pulegone is the chief constituent of oil of pennyroyal (*mentha pulegium*), and was isolated in 1891 by Beckmann and Pleissner, studied by Semmler and Wallach, and ultimately synthesized by Tiemann and Schmidt in 1896.¹ It is separated from

¹ *Ber.*, 1896, 29, 918; 1897, 30, 22.

the crude oil by means of the bisulphite compound and is dextro-rotatory. It forms an oxime and a semicarbazone, a crystalline hydrochloride and hydrobromide, and a characteristic nitroso compound having the double molecular formula $(C_{10}H_{18}ONO)_2$. Finally, on reduction with sodium and alcohol, it takes up two molecules of hydrogen and passes into ordinary menthol. These facts indicate an unsaturated ketone in which the ketone group is determined by its relation to menthol.

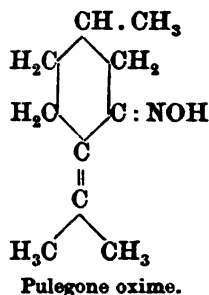
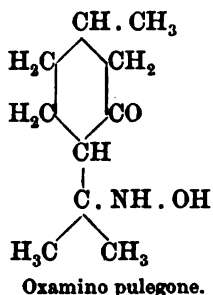


The position of the double bond is also to some extent indicated by the behaviour of pulegone with hydroxylamine. It has been shown by Wallach and others that cyclic ketones with a double bond in the $\alpha\beta$ -position to the ketone group exhibit a characteristic behaviour with hydroxylamine, depending upon whether the double bond is in the nucleus or side-chain. In the former case two molecules of hydroxylamine are utilized, and so-called *oxamino oximes* are formed in which one hydroxylamine molecule forms an additive compound at the double bond, and the other attaches itself to the ketone group.

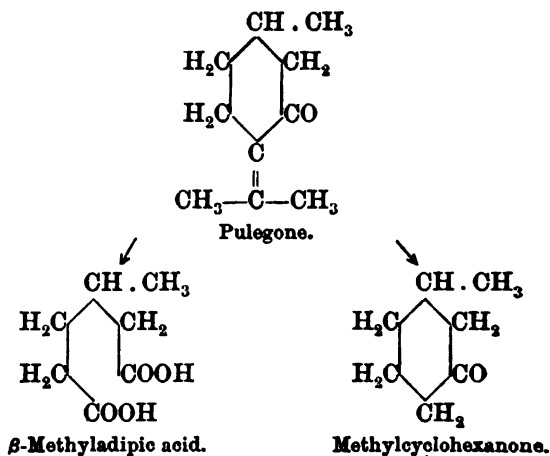


In the second case, where the double bond is in the side-chain, either the additive or oxamino compound is formed, or else the true oxime.

This is the case with pulegone, which forms both an oxime and an oxamino ketone. The double bond lies therefore in the isopropyl side-chain.



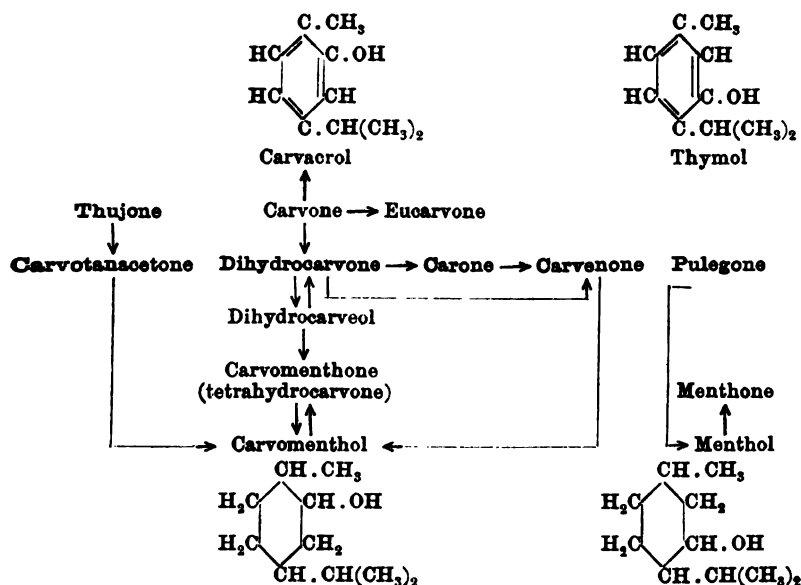
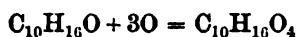
This view also explains its oxidation by permanganate to acetone and β -methyl adipic acid, and its decomposition on heating with formic acid or water to 250° into acetone and methylcyclohexanone.



The table on p. 507 shows the relationships existing between the monocyclic camphors and certain other compounds, which have been discussed in the foregoing section. The camphors are printed in thick type.

Camphor. Common or Japan camphor is one of the oldest known organic compounds. By reason of its crystalline character and easy purification, its extraordinary reactivity, its association with the terpenes and its comparative abundance in nature, it has attracted the attention of more than one generation of chemists. It was analysed by Dumas and found to have the formula $C_{10}H_{16}O$. As early as 1785 its behaviour with nitric acid was studied by Kosegarten, who obtained the acid, now known as *camphoric acid*,

the formation of which was afterwards correctly interpreted by Malaguti, Laurent and Liebig.



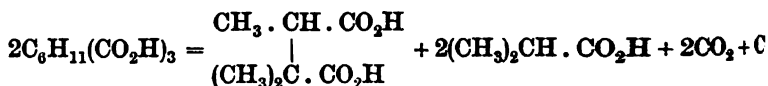
The Monocyclic Camphors and related Compounds.

During the last quarter of a century a host of skilful workers have concentrated their efforts in attempts at discovering its structure, with the result that no less than thirty different formulae have at one time or another been proposed. The earlier formulae were based on the behaviour of camphor with dehydrating and other agents. Phosphorus pentoxide or pentasulphide yield mainly *p*-cymene; zinc chloride produces a variety of aromatic hydrocarbons, among which toluene, *m*-cymene, *m*-xylene, *as*-ethyl-*o*-xylene, and tetramethyl benzene have been identified; hydriodic acid forms tetra- and hexa-hydro-*m*-xylene, and iodine produces considerable quantities of carvacrol (hydroxy-*p*-cymene).

The appearance of so many simple aromatic compounds clearly pointed to a benzene skeleton. It was only necessary to clothe it with suitable groups and side-chains, which should account for the ketonic nature of the compound, the formation of the dibasic camphoric acid, and as many of the aromatic hydrocarbons as their

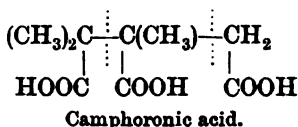
varied nature would admit of, in order to obtain a satisfactory formula. It is clear that the process admitted of varied treatment and some ingenuity. An entirely new light was thrown on the structure of camphor in 1893 by Bredt's¹ discovery of the constitution of camphoronic acid $C_6H_{11}(CO_2H)_3$, which Kachler² had found with camphoric acid among the oxidation products of camphor.

Bredt showed that when camphoronic acid is heated it breaks up into trimethylsuccinic acid and isobutyric acid, whilst carbon dioxide is evolved and some carbon is deposited. This decomposition may be expressed as follows:



Not only is the yield of trimethylsuccinic acid very considerable (60–70 per cent.), but its appearance cannot be ascribed to any secondary process, seeing that Koenigs obtained the same acid by the direct oxidation of camphoric acid with chromic acid.

Camphoronic acid, according to Bredt, is a trimethyltricarballic acid having the following formula:



Its conversion into trimethylsuccinic and isobutyric acid is readily explained by supposing the rupture to occur along one or other of the dotted lines. In the one case two molecules of isobutyric acid will be formed, and in the other, one molecule of trimethylsuccinic acid.

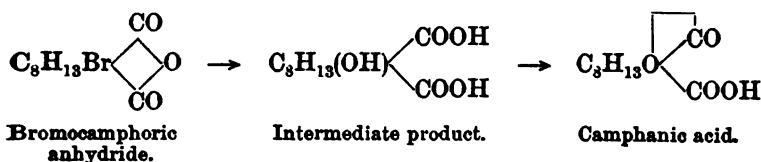
The structure of camphoronic acid has been completely established by Perkin, jun., and Thorpe,³ who obtained it synthetically in the manner described on p. 259. The disposition of nine out of ten carbon atoms is thus accounted for, and as camphoronic acid is also obtained by oxidising camphoric acid, the two must contain the same grouping. Bredt showed that camphoronic acid is also formed when camphanic acid $C_{10}H_{14}O_4$ is oxidised. Camphanic is a lactonic

¹ *Ber.*, 1893, 26, 3047; *Annalen*, 1896, 292, 55.

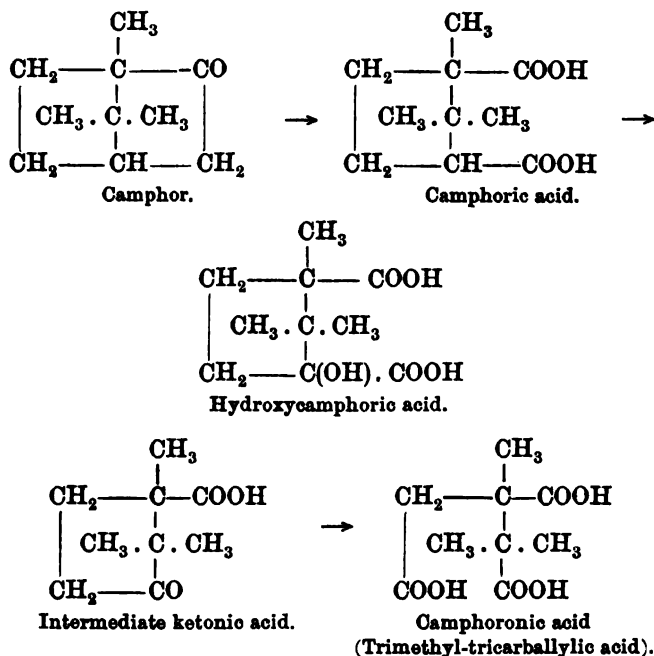
² *Annalen*, 1871, 159, 286.

³ *Trans. Chem. Soc.*, 1897, 71, 1169.

acid derived from hydroxycamphoric acid, and is produced when water or alkalis act upon bromocamphoric anhydride.



According to Bredt the degradation of the camphor molecule on oxidation is represented as follows:

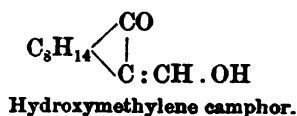
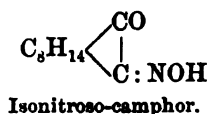


Bredt's formula was accepted with some reserve; for although it represented in a simple and natural fashion the stages in the resolution of the molecule by oxidation, it appeared to break down when submitted to the test of other reactions. Many of the difficulties at first encountered in adopting this formula have since been removed, a result to be mainly attributed to increased familiarity with the properties of 'ring', and more especially 'bridged-ring', structures. The occasion for balancing evidence in favour of one or other formula has fortunately disappeared; for Bredt's formula has received the best possible confirmation in the discovery of Komppa's

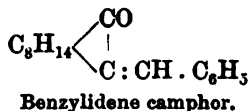
synthesis of camphoric acid. It only remains, therefore, to adjust Bredd's camphor formula to the facts and then to trace as briefly as possible the principal transformations which this many-sided compound undergoes.

1. *Camphor is a ketone*, for it forms an oxime, $C_{10}H_{16}:NOH$, a bromophenylhydrazone, $C_{10}H_{16}:N.NH.C_6H_4Br$, and a semicarbazone, $C_{10}H_{16}:N.NHCONH_2$. On reduction it yields the secondary alcohol, borneol, $C_{10}H_{17}OH$, and when heated with ammonium formate, the base bornylamine, $C_{10}H_{17}NH_2$, which is also formed when camphoroxime is reduced.

2. *Camphor contains the group* $-CH_2.CO-$. Claisen and Manasse prepared an isonitroso derivative and a hydroxymethylene camphor by the usual methods (see p. 288).

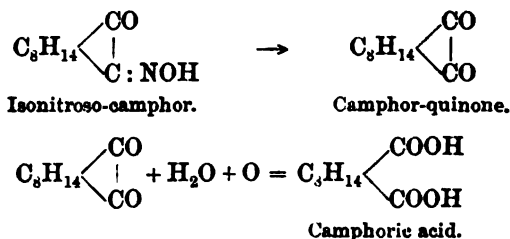


It also forms with benzaldehyde and its derivatives benzylidene compounds of the following type:



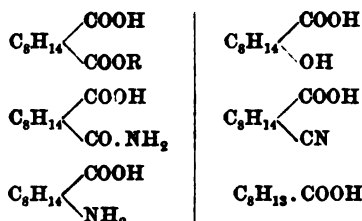
All these reactions are associated with the above $-CH_2.CO-$ group.

8. *The group* $-CH_2.CO-$ *is transformed into the two carboxyls of camphoric acid*. Claisen and Manasse showed that isonitroso-camphor, on hydrolysis, yields camphor-quinone, which, on oxidation, is converted easily and completely into camphoric acid.



Moreover, the two carboxyl groups are differently disposed, for there exist two series of acid esters (known as *ortho* and *allo* or α and β); two camphoramides, two amino acids, two hydroxy and two cyano acids, and also a corresponding series of four un-

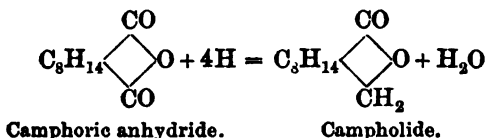
saturated monobasic acids, $C_8H_{13} \cdot COOH$, known as α -campholytic, β - or cis-campholytic (or isolaunonic) acid, allo-campholytic (or launonic) acid, and an isomeric launonic acid, all of which will be described later (p. 518).



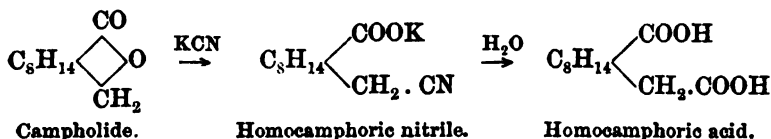
The *ortho* and *allo* (α and β) series of Camphoric acid derivatives.

The relation of camphoric acid to camphor is further established by the experiments of Haller,¹ who succeeded in transforming camphoric anhydride into camphor in the following way:

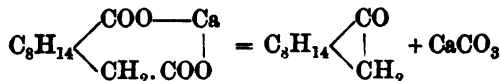
Camphoric anhydride can be reduced with sodium amalgam to campholide.



Campholide, when heated with potassium cyanide, yields the nitrile of homocamphoric acid.



Finally, the calcium salt is heated, and camphor distils.

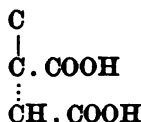


There are other ways of preparing homocamphoric acid directly from camphor, but they do not possess the theoretical interest which attaches to the synthesis from camphoric acid. It is a significant fact that whilst camphoric acid, like the succinic and glutaric acids, yields an anhydride on heating, homocamphoric acid does not, and consequently the carboxyls in the latter must be separated by at

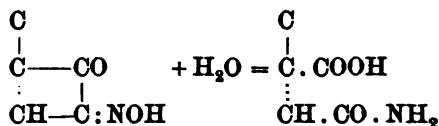
¹ *Compt. rend.*, 1896, 122, 446.

least a four-carbon chain. It follows that camphoric acid, which is the lower homologue, must possess a three-carbon chain or glutaric acid structure.

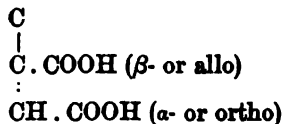
The structural relations between camphor and camphoric acid being thus clearly established, we have still to ascertain the cause which underlies the difference in the disposition of the two carbonyl groups, and to discover which of these two groups corresponds to the ketone and which to the methylene group in camphor. Chemical and physical evidence combine to prove that both camphor and camphoric acid are saturated compounds. By the action of bromine on camphoric anhydride substitution takes place, but only one monobromo derivative, ω -bromocamphoric acid, is formed. As bromine always attaches itself to the α -carbon in an acid, there can be but one α -hydrogen, and camphoric acid will probably contain the group:



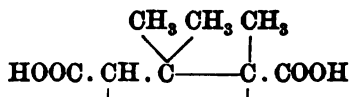
The differentiation of the α - and β -series is arrived at in the following manner: when isonitroso-camphor is warmed with hydrochloric acid it is converted into camphoraminc acid of the α -series.



It is the methylene group, therefore, which represents the α -carbonyl in camphoric acid.

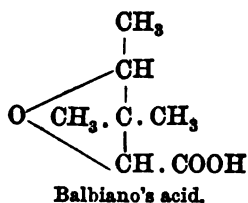


4. *Camphoric acid contains a trimethylglutaric group:*

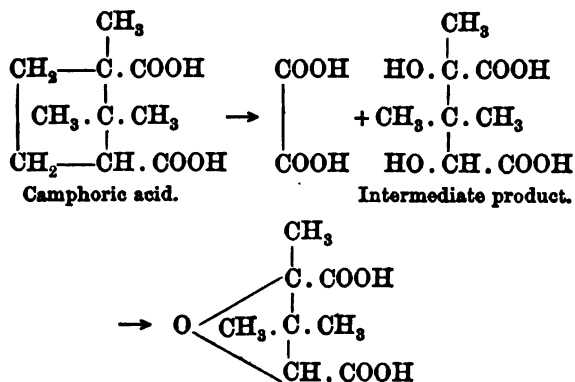


An important clue to the structure of camphoric acid was afforded by the researches of Balbiano. By oxidising camphoric acid with permanganate very slowly at the ordinary temperature, thereby

excluding the likelihood of intramolecular change, he obtained, in addition to small quantities of camphanic, camphoronic, and trimethylsuccinic acids, a dibasic acid, $C_8H_{12}O_6$, and an equivalent quantity of oxalic acid as the chief products. This new acid, on reduction with hydriodic acid, gave, among other products, an acid, $C_8H_{14}O_4$, which was identified as $\alpha\beta$ -trimethylglutaric acid, afterwards prepared synthetically by Perkin and Thorpe.¹ Balbiano's acid does not possess ketonic properties, for, although it combines with hydroxylamine and hydrazines, the products are of the nature of additive compounds, and the compound almost certainly represents the inner ether of a dihydroxytrimethylglutaric acid, having the structure,



Its appearance in company with oxalic acid is very simply explained by the aid of Brett's formula:

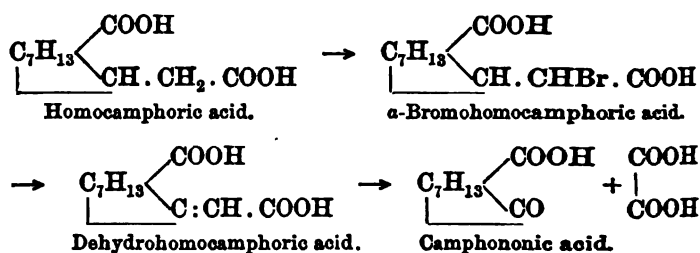


5. *Camphoric acid is a derivative of Cyclopentane.* The presence of a 5-carbon ring in camphoric acid appears very probable when the following evidence is considered. Lapworth² showed that when homocamphoric acid is brominated and hydrobromic acid then

¹ *Trans. Chem. Soc.*, 1899, 75, 61.

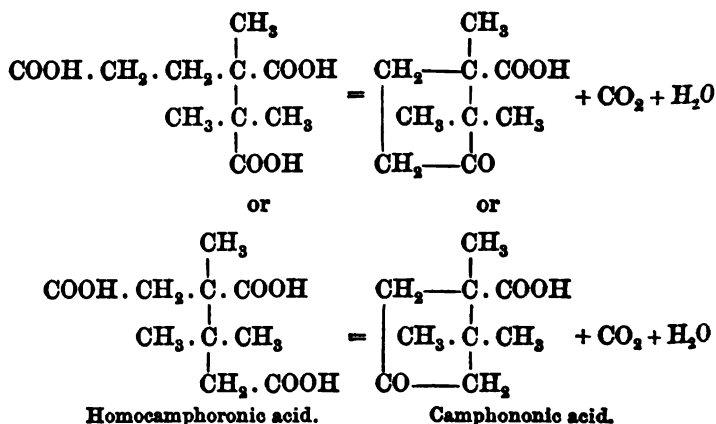
² *Trans. Chem. Soc.*, 1900, 77, 1053.

removed, an unsaturated dehydrohomocamphoric acid is formed which yields oxalic and camphononic acid on oxidation.

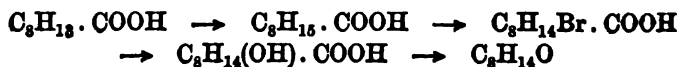


Now camphononic acid is a saturated ketonic acid which may also be obtained by heating the anhydride of homocamphoronic acid to 200–260°.

Homocamphoronic acid, which is probably represented by one of the following structural formulae, yields camphononic acid as follows :

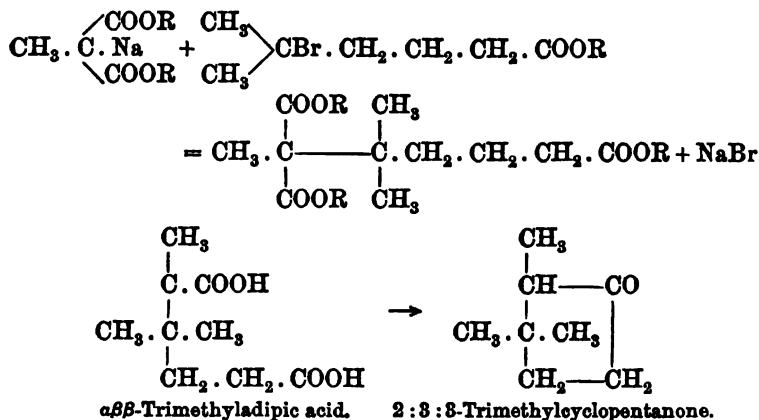


Another piece of evidence of a similar nature has been contributed by Noyes.¹ Isolaunonic acid (see p. 520) gives on reduction a dihydro-derivative in which one α -hydrogen can be replaced by bromine. By the action of baryta on the bromine compound a hydroxy-dihydro-isolaunonic acid is obtained which, on oxidation, loses carbon dioxide and forms a ketone.

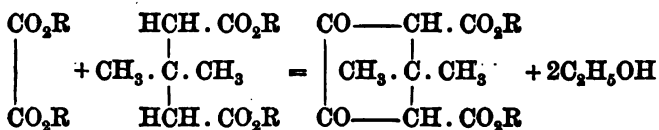


¹ Ber., 1899, 32, 2283.

This ketone was synthesized and identified as 2:3:3-trimethylcyclopentanone in the following way: by combining sodium methyl malonic ester with γ -bromoisocaproic ester, the ester of a tribasic acid was obtained which, on hydrolysis, gave the acid. This acid loses carbon dioxide on heating, and passes into $\alpha\beta\beta$ -trimethyladipic acid, the lime salt of which is converted by heat into the ketone in question.

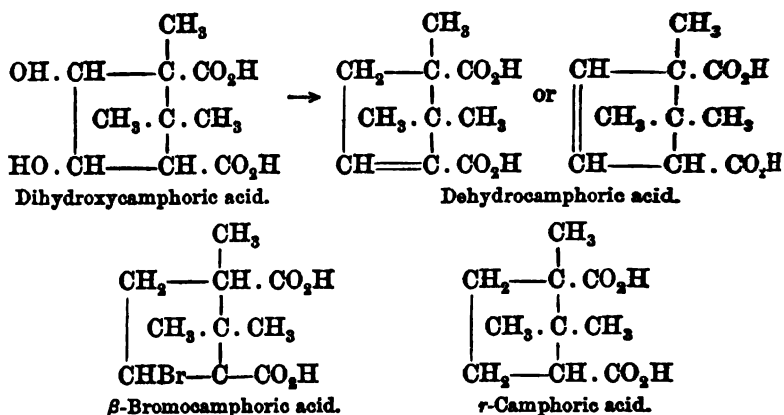


6. *Komppa's synthesis of camphoric acid.* This synthesis affords the most convincing proof of the correctness of Bredt's formula. Ethyl-diketoapocamphorate, which is the starting-point, was prepared by Komppa¹ by condensing ethyl oxalate with ethyl $\beta\beta$ -dimethylglutarate (p. 267).



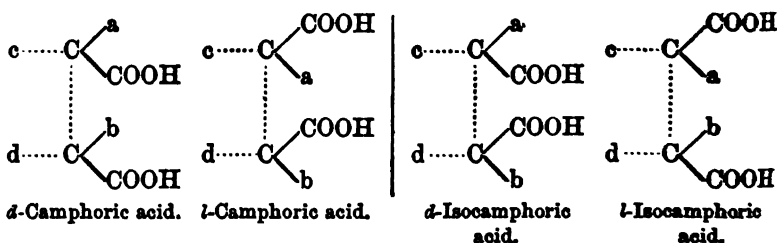
A methyl group was then introduced by the action of sodium and methyl iodide. The product was reduced to dihydroxycamphoric acid, and then boiled with hydriodic acid and red phosphorus and converted into the unsaturated acid, dehydrocamphoric acid. The latter combines with hydrobromic acid, and forms a β -bromocamphoric acid, and is then reduced with zinc dust and acetic acid to *r*-camphoric acid, which is identical with the racemic product obtained from camphor by oxidation.

¹ Ber., 1901, 34, 2472; 1903, 36, 4832.



Having now reviewed the principal evidence in favour of Bredt's formula for camphor, we will proceed to criticize it in the light of some of its less salient but not less important features.

Both camphor and camphoric acid are optically active. Camphor is found in two enantiomorphous forms, Japan camphor being dextro-rotatory, and Matricaria camphor laevo-rotatory; camphoric acid has been obtained in four active modifications, a *d*- and *l*-camphoric acid and a *d*- and *l*-isocamphoric acid,¹ and two racemic compounds derived from them. The *d*- and *l*-camphoric acids are obtained from the two active camphors by oxidation, and each can be converted into the corresponding isocamphoric compound. The formula for camphoric acid harmonizes with the existence of two pairs of active enantiomorphs, for it contains two asymmetric carbon atoms. The four active compounds may be represented as follows:

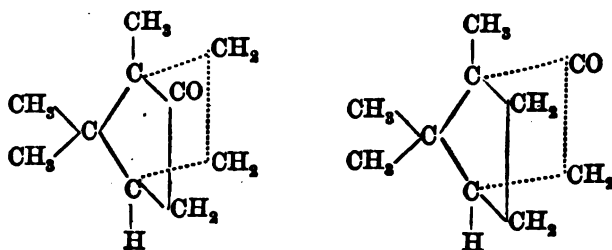


The first pair have a *cis*, the second a *trans* configuration, and in accordance with the theory the former yield anhydrides, whereas the latter do not.

The reason for the existence of only two active camphors is not so obvious, for camphor contains the same two asymmetric carbon

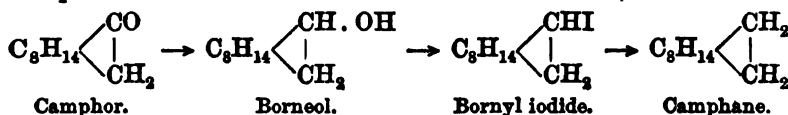
¹ Aschan, *Ber.*, 1894, 27, 2001; *Annalen*, 1901, 316, 196.

atoms as camphoric acid. There is, however, this difference, that the two carbon atoms, which in camphoric acid are represented by carboxyls and are free to assume independent positions, are linked together in camphor. It follows that there are only two active camphors which correspond to *d*- and *l*-camphoric acid, and may be represented in the following manner:



d- and *l*-Camphor.

It will at once be obvious that the asymmetry of the camphor molecule as represented above depends on the presence of the ketone group. That this is the case has been demonstrated by Aschan,¹ who succeeded in converting the ketone group by reduction into a methylene group in the manner indicated below, with the object of producing a completely symmetrical and consequently inactive compound.

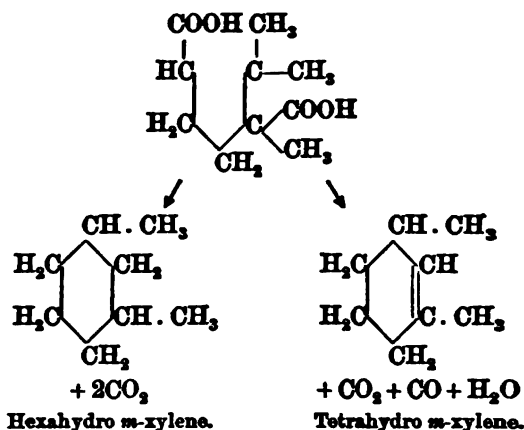


The reduction was carried out in such a way as to preclude racemisation, with the result that the hydrocarbon camphane was quite inactive.

Some of the opposition which Bredt's formula at one time encountered was due to the difficulty of reconciling it with the production of substances like *m*-xylene and its tetra- and hexahydro-derivatives. The formation of the various benzene hydrocarbons, though it must remain more or less a matter of conjecture owing to the difficulty of following the changes in detail, is readily explained, since it is now a well established fact that under certain conditions the methyl side-chain of a cyclopentane derivative may become fused into the ring of a cyclohexane compound. The conversion of camphoric acid into derivatives of *m*-xylene may very well take place in accordance with the following scheme:

¹ *Annalen*, 1901, 316, 229.

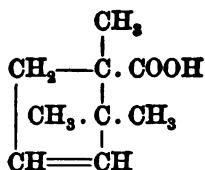
THE CAMPHORS



But the real stumbling-block which has stood longest in the way of the Bredt formula has been the intractable nature of isolauronolic and β -campholenic acids. In order to understand the position occupied by these acids it is necessary to consider them in conjunction with their isomers from the point of view of their preparation, as well as of their properties. An acid of the formula $\text{C}_8\text{H}_{13} \cdot \text{COOH}$, called lauronolic acid, was first observed by Fittig and Woringer.¹ It is obtained by the action of water or alkalis on bromocamphoric anhydride, or by the dry distillation of camphanic acid (see p. 509).



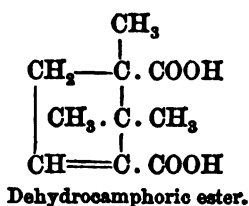
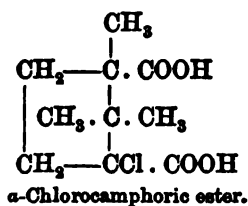
These reactions appear to point to the following formula:



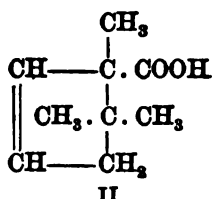
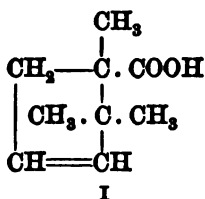
But this acid should give camphoronic acid on oxidation (p. 508), which it does not, but on the contrary forms a variety of other products, quite irreconcilable with the above structure.² A second lauronolic acid was obtained by Bredt from α -chloro-camphoric ester, which on treatment with quinoline loses hydrogen chloride, and gives the ester of an unsaturated dibasic acid (dehydro-camphoric acid), from which carbon dioxide can be removed on heating and lauronolic acid generated.

¹ *Annalen*, 1885, 227, 1.

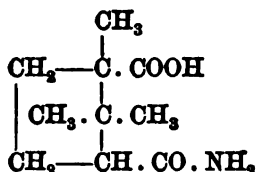
² *Ber.*, 1900, 33, 2949.



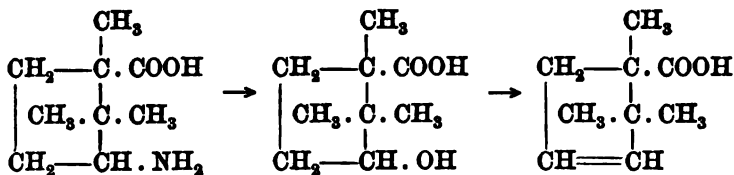
As Bredt's acid gives camphoronic acid on oxidation it must have the structure originally assigned to the previous compound I, whilst Fittig and Woringer's acid will probably be represented by II.



The structure of Bredt's acid is also in agreement with its formation from α -camphoramic acid. The latter is obtained by the action of ammonia on camphoric anhydride, and its constitution is determined by its production from isonitrosocamphor (see p. 510).



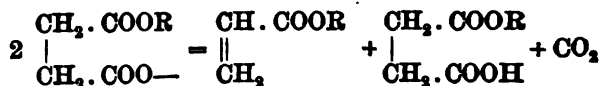
From it Noyes obtained by the action of sodium hypobromite the amino acid, which nitrous acid converts partly into the hydroxy-derivative, partly, by elimination of a molecule of water, into lauronolic acid.



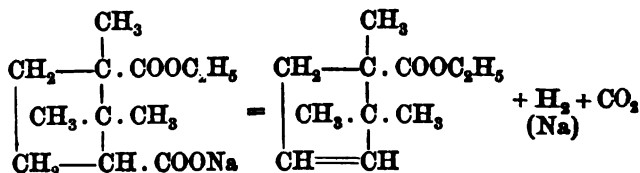
The same acid has also been obtained by Walker¹ by the electrolysis of the sodium salt of the allo ethyl ester of camphoric acid

¹ *Trans. Chem. Soc.*, 1898, 63, 495; 1895, 67, 837.

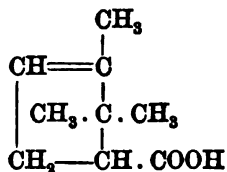
(see p. 510). According to the usual behaviour of dibasic acid esters under the influence of the current, carbon dioxide is split off, and together with certain other products an unsaturated acid is formed. Ethyl sodium succinate gives acrylic ester.



The formation of lauronolic acid takes place in accordance with a similar scheme :



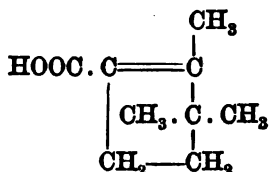
By the same process Walker converted the sodium salt of the ortho ethyl ester into a mixture of α -campholytic and isolauronolic (cis-campholytic) acids, and Noyes obtained the same two acids from β -camphoramie acid by repeating the same series of changes which produced lauronolic acid from the α -compound. As isolauronolic acid is easily obtained from the α -compound by boiling with dilute sulphuric acid they have been regarded as stereoisomeric; but this is doubtful. Assuming it to be the case, the natural inference would be that both acids possess the formula,



but here a difficulty arises, for the isolauronolic acid is undoubtedly an $\alpha\beta$ -unsaturated acid. It is inactive, which would scarcely be the case if the above formula held, seeing that it contains one of the original asymmetric carbon atoms of camphoric acid undisturbed, and it cannot be resolved into active constituents; it forms a dibromide from which alkalis remove not only hydrobromic acid but also carbon dioxide, a change which Fittig's researches have shown to be characteristic of $\alpha\beta$ -unsaturated acids. Furthermore, dihydro isolauronolic acid, obtained from the original acid by reduction, gives on bromination a monobromo derivative, from which alkalis remove

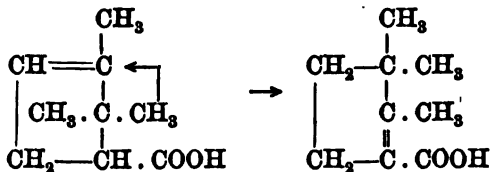
hydrogen bromide and regenerate isolaunonic acid. As the bromine substitutes hydrogen in the α -position to the carboxyl the double link must necessarily occupy the $\alpha\beta$ -position.

The synthesis of isolaunonic acid by Perkin and Thorpe¹ has fixed the structure beyond all doubt.



Isolaunonic acid.

But how is such a structure to be reconciled with its formation from β -camphoramic and ortho camphoric ester? A very simple explanation has been suggested by Blaise and Blanc² and by Lapworth,³ which is based upon a change similar to the pinacone-pinacoline conversion (see p. 209). Supposing in the above structure one of the 1:1-methyl groups passed to the adjoining carbon with a corresponding readjustment of the double bond, an acid of the required formula is produced.



The difficulty involved in dealing with such mobile complexes as camphor and its degradation products is further illustrated by the behaviour of isolaunonic acid on oxidation. According to Koenigs and Meyer⁴ it yields isolaunonic acid, $\text{C}_9\text{H}_{12}\text{O}_3$, which Perkin, jun.,⁵ characterized as a ketonic acid, and Blanc⁶ identified as a cyclohexane derivative. Blanc's view was arrived at from the observation that isolaunonic acid on reduction forms a dihydro derivative, $\text{C}_9\text{H}_{14}\text{O}_3$, which on heating with sodium hypobromite loses carbon dioxide and gives *aa*-dimethyladipic acid. These changes are explained as follows :

¹ *Trans.*, 1904, 85, 128.

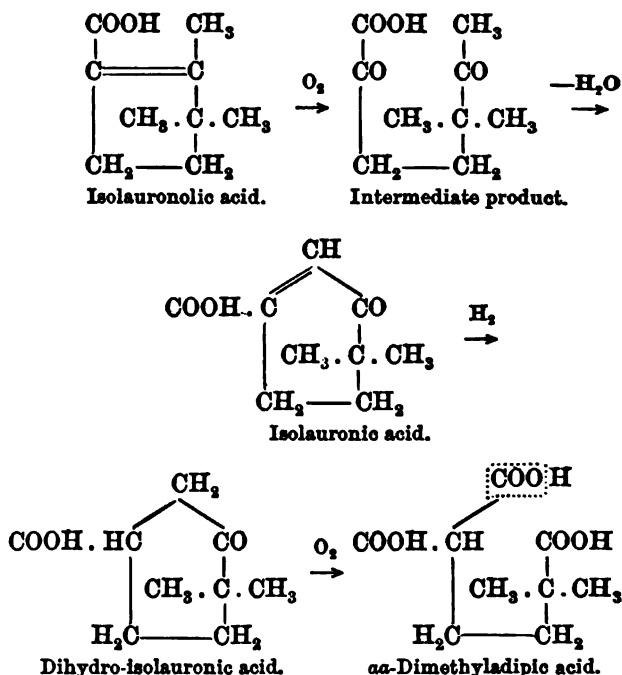
² *Bull. Soc. Chim.*, 1900 (3), 23, 167.

³ *B. A. Reports*, 1900, 825.

⁴ *Ber.*, 1894, 27, 8466.

⁵ *Trans. Chem. Soc.*, 1898, 73, 802.

⁶ *Compt. rend.*, 1900, 130, 840.



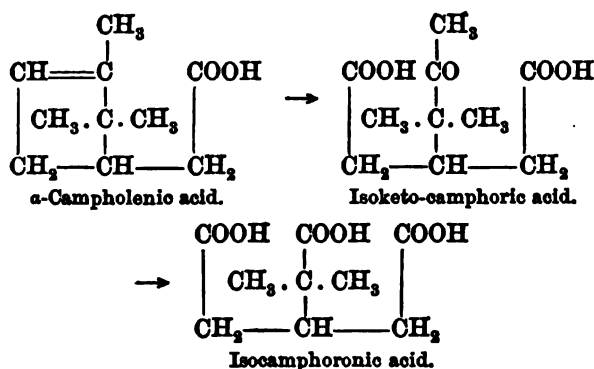
It is only another case of the convertibility of cyclopentane and cyclohexane structures (see p. 517).

The theory of the formation of isolauronolic acid has served to explain the structure of β -campholenic acid. There are two, α - and β -campholenic acids. They can be obtained in a variety of ways, as, for example, by the dehydration of camphoroxime, which yields the nitriles of the two acids in question.

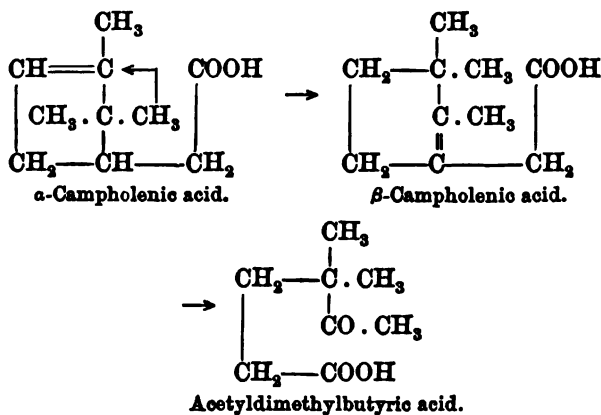


Like α -campholytic acid, α -campholenic acid can be converted by the aid of different reagents into the β -compound, which is probably a secondary product of the above reaction. The structure of the α -compound offers no difficulty. It is dextro-rotatory, and contains, therefore, an asymmetric carbon; it gives, on oxidation, successively a dihydroxy derivative, isoketo-camphoric acid, and finally isocamphoronic acid, the structure of which has been ascertained by synthesis (p. 289).¹ All these changes are expressed simply and naturally as follows:

¹ Perkin, jun., *Trans. Chem. Soc.*, 1899, 75, 897.



The β -acid, on the other hand, is inactive, and yields an inactive dihydroxy derivative on oxidation, which subsequently breaks up into oxalic acid and γ -acetyldimethylbutyric acid. The appearance of these two acids in conjunction with a structure which contains no asymmetric carbon is at first a little perplexing; but the observation that isolaunonic acid gives the same γ -acetyldimethylbutyric acid has suggested the homology of the two acids and the probability of a similar shifting of a methyl group in the formation of the β - from the α -compound.

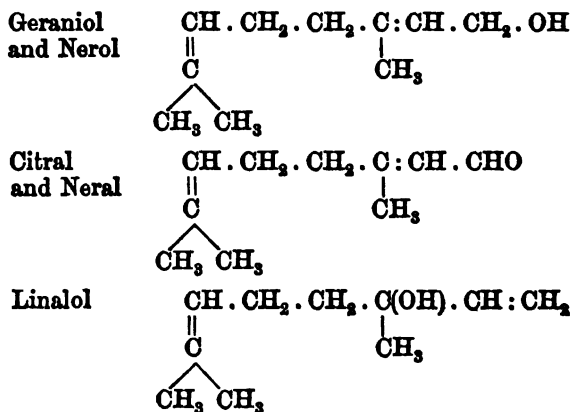


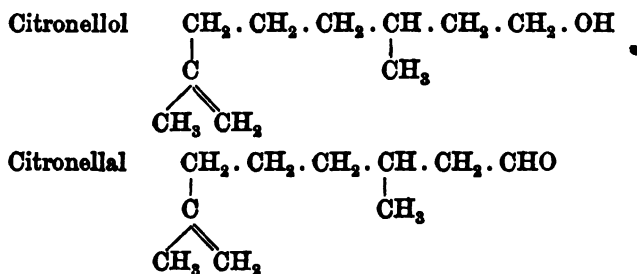
Our account of camphor must draw to a close. The manifold changes of this mobile molecule—a veritable Proteus among organic compounds—are far from being exhausted, but the reference books must be consulted for further information. Our object in the foregoing account has merely been to give the reader some idea of the transformations which camphor and its products undergo under different conditions, and to throw some light on the difficulties which

have attended the inquiry into its structural formula. The discovery of the constitution of camphor has now been accomplished, and the experience thus gained has vastly increased our knowledge of cyclic structures.

The Olefinic Terpenes and Camphors. The constituents of the essential oils which have been described in the previous section belong to saturated or unsaturated cyclic systems; but in recent years a new group of open-chain compounds of the formula $C_{10}H_{16}$, $C_{10}H_{16}O$, and $C_{10}H_{18}O$ has been discovered and described by Tiemann and Semmler, and named by them *olefinic terpenes and camphors*. The name does not merely indicate similarity in composition with the terpenes and camphors, but a very close relationship in chemical structure. Moreover, they have been recognized as responsible in a great measure for the delicate aroma of these essential oils in which they occur. The perfume of orange-blossom, rose, and lavender is due to the presence of minute quantities of these substances. They exhibit among themselves a certain similarity in structure and, at the same time, show an unmistakable connection with the terpene and camphor group. They contain ten carbon atoms, which are disposed in such a way that six form a straight chain, three of them form an unsaturated isopropyl group attached to one end of the chain, and the tenth a methyl group at the fourth carbon atom from the end of the chain. In other words, the grouping may be conceived to resemble that of a monocyclic terpene or camphor in which the ring has been ruptured.

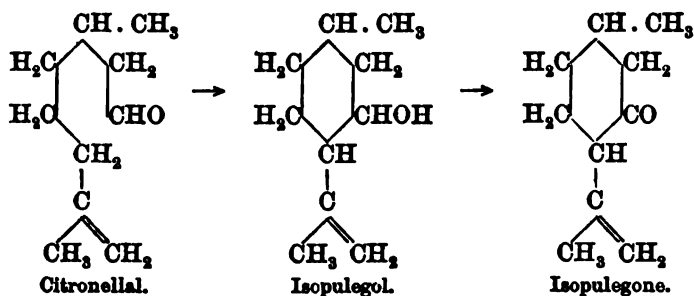
The following is the probable structure of some of these compounds:



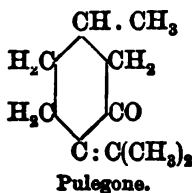


This conception is not a purely theoretical one, for we shall see presently that cyclic terpenes can be prepared by simple methods from these compounds, and, by a reversal of the process, certain cyclic compounds may be converted into open-chain members of the group.

Thus, citronellal when heated with acetic anhydride changes into isopulegol, and on oxidation into isopulegone,



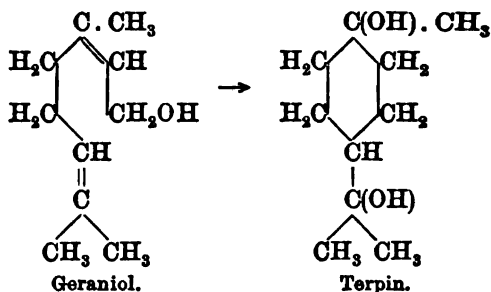
and the latter, by the action of baryta, undergoes isomeric change to pulegone.



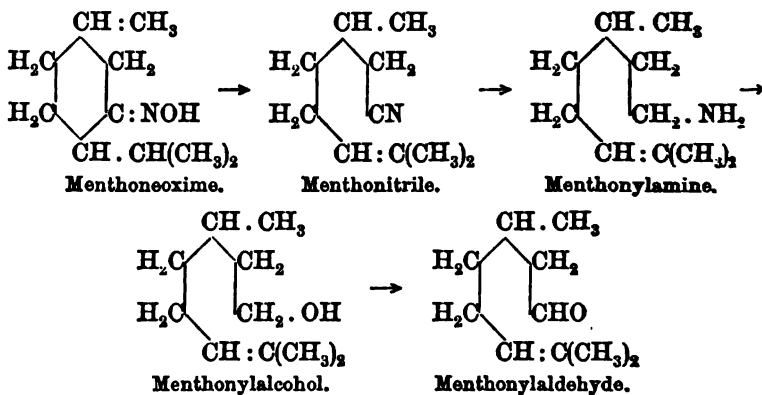
Linalol in presence of formic acid at 80° is converted into a mixture of dipentene and terpinene.¹ This change is doubtless brought about in the first instance by the isomeric change of linalol to geraniol, which acids are known to effect. By the removal and subsequent

¹ *J. prakt. Chem.*, 1892 (2), 45, 601.

addition of the elements of water, ring formation occurs with the production of terpin, followed by that of dipentene and terpinene.



An example of formation of an open-chain structure from a cyclic ketone is presented by menthone, which by the following series of operations yields a product isomeric and possibly identical with citronellal and having the perfume of roses. The ketone is converted into the oxime, which by dehydration gives menthonitrile. The latter is reduced in the ordinary way to menthonylamine, which is then decomposed by nitrous acid. The alcohol thus formed, is oxidised to the aldehyde.



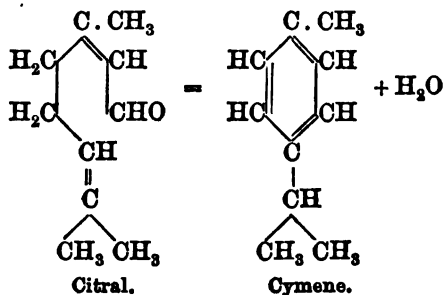
The importance of the olefinic terpenes and camphors from an industrial point of view cannot be estimated too highly; for the aroma of many perfumes is undoubtedly due to their presence. Their scientific study, which is intimately linked with the industry of the essential oils, has prepared the way for new developments in synthetic chemistry.

The following is a brief description of the more important members of this group of compounds:

Geraniol. In 1890 Semmler showed that the alcohol isolated by

Jacobsen¹ in 1871 from Indian geranium oil (by means of the solid compound which it forms with calcium chloride), and having the formula $C_{10}H_{18}O$, was not a cyclic compound; but by reason of the additive compound which it forms with bromine, and its constant of refraction, must contain two double bonds, and was in all probability an unsaturated open-chain compound. Geraniol is widely diffused, being found in German and Turkish rose oil, in citronella and lemon-grass oils, and in smaller quantities in ylang-ylang, lavender, and other essential oils. On careful oxidation with chromic acid mixture it is converted into an aldehyde, citral, a substance which is also found in nature in different kinds of lemon oil.² As geraniol can be obtained from citral by reduction, and as citral has been prepared artificially (see below), geraniol must also be ranked among synthetic products. It is further obtained from linalol, which undergoes isomeric change on heating with acetic anhydride, and conversely, geraniol can be transformed into linalol by heating with water to 200° , whilst certain dehydrating agents, like potassium hydrogen sulphate, convert geraniol into the olefinic terpene *geraniene*, $C_{10}H_{16}$; formic acid produces dipentene and terpinene, and a mixture of acetic and sulphuric acid forms terpineol (m.p. 85°). The structure of geraniol depends upon that of citral.

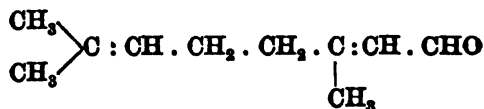
Citral (geranial) is a common constituent of essential oils, and it is to this substance that lemon oil owes its delicate aroma. It is very abundant in lemon-grass oil (70–80 per cent.), and is an important constituent of orange, mandarin, limette, and certain kinds of eucalyptus oil. It is a di-olefinic aldehyde, for it gives the usual reactions for aldehydes, including its conversion into *geranic acid* on oxidation, and it also unites with two molecules of bromine. It is very sensitive to acid reagents, and by the action of dilute sulphuric acid and potassium bisulphate it loses water and passes into cymene.



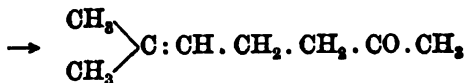
¹ *Annalen*, 1871, 157, 232.

² Semmler, *Ber.*, 1891, 24, 201.

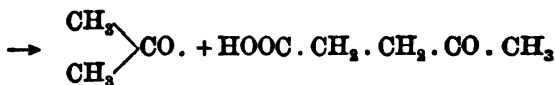
Its structure is derived from its behaviour with chromic acid mixture, which breaks it up into methylheptenone in the first instance, and finally into acetone and levulinic acid,



Citral.



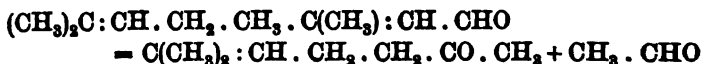
Methylheptenone.



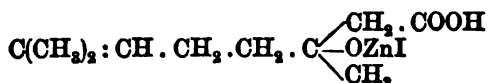
Acetone.

Levulinic acid.

and also from its conversion into methylheptenone and acetaldehyde by the action of potassium carbonate.



The syntheses of citral and geranic acid which confirm the above formula have been effected by Barbier and Bouveault¹ from methylheptenone in the following way: the latter reacts with zinc and iodacetic acid (p. 258), giving the compound,



which is converted on the addition of dilute acid into the hydroxy acid,



losing water and yielding geranic acid on distillation with acetic anhydride. By distilling the calcium salt of geranic acid with calcium formate Tiemann² obtained citral.

Linalol is widely distributed, and occurs in optically active forms. It is dextrogyrate in coriander oil, but in no other oil, whereas the laevo compound is found partly free and partly as linalyl acetate in the oils of linaloes, bergamot, neroli, petitgrain, limette, spike, lavender, sage, thyme, spearmint, origanum, ylang-ylang, &c. It readily undergoes change with acids; organic acids convert it into the isomeric geraniol, whilst small quantities of sulphuric acid pro-

¹ *Compt. rend.*, 1896, 122, 893.

² *Ber.*, 1893, 31, 837.

luce terpineol, and by shaking with 5 per cent. sulphuric acid erpin hydrate is formed. Its conversion into dipentene and terpinene has already been described (p. 525).

Its close connection with geraniol, combined with its optical activity, indicates the formula given on p. 524.

Citronellol contains two atoms of hydrogen more than geraniol and linalol. It is found in geranium oils in both active forms, the laevogyrate predominating. Mixed with geraniol it is present in various rose oils. It can also be prepared artificially from the aldehyde citronellal by reduction.

Citronellal, the chief constituent of citronella oil (from *Andropogon nardus*) and oil of *Eucalyptus maculata*, is frequently found accompanying citral in lemon and rose oil, from which, however, it is easily distinguished by its optical activity. Its structure is determined by oxidation, which breaks it up into acetone and β -methyladipic acid. It is an interesting fact that acetic anhydride converts citronellal into the isomeric isopulegol, which can be transformed successively into isopulegone and the natural pulegone (p. 525).

Nerol, which is found in neroli and petitgrain oil, and its oxidation product, *nerul*, are probably stereoisomeric with geraniol and citral.¹

Natural and Artificial Perfumes. The history of perfumes and essences carries us back to very remote times, but the scientific study of the chemical nature of the substances which afford the aroma is of comparatively recent date, and may be said to have begun with the researches of Wallach and Tiemann a quarter of a century ago. The results of some of these investigations have been presented in the foregoing pages, in which the properties of the terpenes and camphors and their olefinic analogues are described, but the list of aroma-bearing constituents of plants is by no means complete. Some of the simpler aromatic compounds, like oil of bitter almonds (benzaldehyde), oil of wintergreen (methyl salicylate), methyl anthranilate, thymol, carvacrol, eugenol, vanillin, coumarin, saffrole, anethole, and many other natural perfumes have not been included, and little, if anything, has been said on the subject of their artificial preparation. The knowledge that a peculiar perfume had its origin in a definite chemical individual which could be isolated in a pure and therefore concentrated form, the development of analytical processes which effected the separation of these constituents, and finally the attempts, which in many cases were carried to a successful issue, of producing

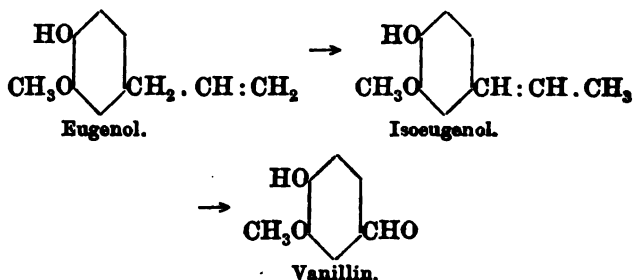
¹ Zeitschel, *Ber.*, 1906, 39, 1780.

the aroma-bearing substance artificially, have given an extraordinary impetus to the development of the perfume industry, especially by chemical manufacturers in Germany. The history of this development is only another instance of the successful application of pure science to technology, of which the artificial colour industry is a striking example.

We do not propose to do more than to give a brief account of some of the more important natural and artificial perfumes not included among the substances already described. Shortly after Mansfield's discovery of the production of nitrobenzene from benzene in 1847, Collas introduced it as 'essence of mirbane' into commerce. A few years later the esters of the fatty acids appeared as apple, pine-apple, pear essences, &c. In 1844 Cahours found that methyl salicylate was the chief constituent of wintergreen oil, and this discovery soon led to its artificial preparation from synthetic salicylic acid.

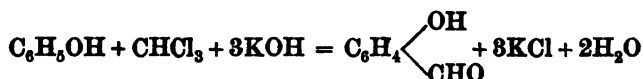
In 1868 Cahours found a process for preparing benzaldehyde from benzal chloride, and this discovery was the forerunner of other artificial aldehydes with characteristic scents; in 1875 Perkin obtained coumarin synthetically (p. 279); in 1888 artificial musk (trinitro- ψ -butyltoluene) was discovered by Baur, and other strongly scented di- and tri-nitro compounds have since appeared.

The first synthesis of vanillin, the sweet-smelling constituent of the vanilla pod, of which it constitutes about 1 per cent., was accomplished by Tiemann and Haarmann in 1875. It was obtained by oxidising coniferyl alcohol, a constituent of the glucoside, coniferin (p. 849). In the following year coniferyl alcohol was replaced by eugenol, which is present to the extent of 70-90 per cent. in oil of cloves. Eugenol is first converted by boiling amyl alcoholic potash into isoeugenol, which is then oxidised to vanillin.

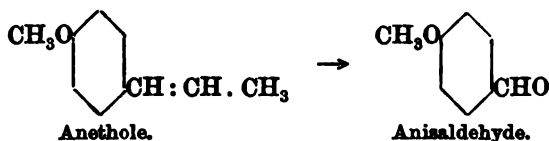


Since then a dozen different methods have been devised for preparing this substance, and are described in books of reference.

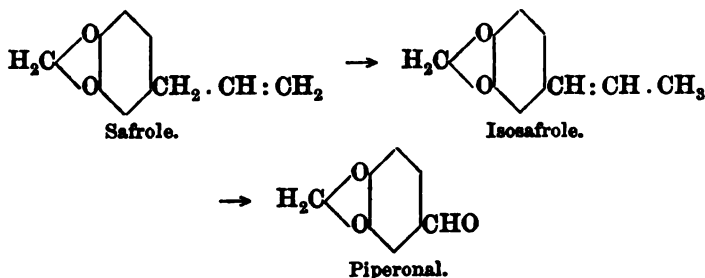
Of the many artificial aldehydes which are used as perfumes the following may be mentioned: *cuminaldehyde* gives the odour to *cumin oil*; *salicylaldehyde* is present in *spiraea oil*, and is obtained artificially by the action of chloroform and potash on phenol by *Reimer's reaction*, and by other methods.



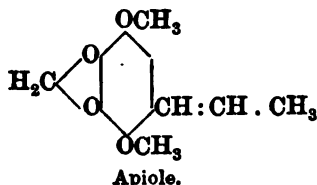
Anisaldehyde is prepared by the oxidation of *anethole*, the chief constituent of *anise oil*, and has the odour of *hawthorn*.



Cinnamic aldehyde or *cinnamol* is the chief constituent of *cinnamon* and *cassia oil* (75–90 per cent.); *piperonal* or *heliotropin* is obtained from *safrole*, which is first converted into *isosafrole* and then oxidised, and possesses the scent of *heliotrope*.



Apiole is an ether related to *safrole*, and is the aromatic constituent of *parsley seed oil*.



The aliphatic ketones which are found in nature, and have been prepared artificially, include *methylheptenone*,



which smells like *amyl acetate* and *methyl nonyl ketone*, $\text{CH}_3 . \text{CO} . \text{C}_9\text{H}_{19}$, which imparts the scent to *oil of rue*.

The natural cyclic ketones play a very important rôle as perfumes, and many of them have already been described (p. 504). The most interesting is *ionone*, the natural perfume of the violet, which has been so closely imitated in the form of ionone by Tiemann, both in structure and scent, as to rank among the crowning achievements in organic synthesis (p. 275).

Chavicol and *estragol* are related to anethole, and accompany it in aniseed and other oils.

Among recent discoveries in the chemistry of perfumes is that of methyl anthranilate and indole, both of which impart their aroma to jasmine, whilst methyl anthranilate is also present in neroli, lemon and several other essential oils.

The following table contains some typical examples of essential oils and their chief constituents. The less important constituents are bracketed.

<i>Name.</i>	<i>Source.</i>	<i>Constituents.</i>
Anise oil.	<i>Pimpinella anisum</i> .	Anethole, estragol (anise aldehyde and 'anise ketone').
Bay oil.	<i>Pimenta acris</i> .	Eugenol, myrcene $C_{10}H_{16}$, chavicol, methyl eugenol, estragol, phellandrene.
Bergamot oil.	<i>Citrus bergamea</i> .	Linalyl acetate, linalol, α -limonene, bergaptene $C_{15}H_{24}$.
Cassia oil.	<i>Cinnamomum cassia</i> .	Cinnamic aldehyde, cinnamyl acetate (cumaric aldehyde, methyl ether).
Caraway oil.	<i>Carum carvi</i> .	Carvone (α -limonene).
Camphor oil.	<i>Cinnamomum camphora</i> .	α -Pinene, phellandrene, dipentene, cadinene $C_{15}H_{24}$, eugenol, safrole, terpineol, acetaldehyde, cineol.
Chamomile oil (Roman).	<i>Anthemis nobilis</i> .	Isobutyl, isoamyl, and hexyl esters of isobutyric, angelic, and tiglic acids.
Cinnamon oil (Ceylon).	<i>Cinnamomum Zeylanicum</i> .	Cinnamic aldehyde (eugenol).
Clove oil.	<i>Eugenia caryophyllata</i> .	Eugenol (caryophyllene $C_{15}H_{24}$, eugenol acetate, furfural, methyl alcohol, salicylic acid).
Coriander oil.	<i>Coriandrum sativum</i> .	Linalol (α -pinene).
Cumin oil.	<i>Cuminum cyminum</i> .	Cumic aldehyde (cuminal), γ -mene.
Eucalyptus oil.	<i>Eucalyptus globulus</i> .	Cineol, α -pinene (butyric, valeric, and caproic aldehydes).
Fennel oil.	<i>Foeniculum vulgare</i> .	Anethole, fenchone, dipentene, α -pinene.
Geranium oil (East Indian).	<i>Andropogon schoenanthus</i> .	Geraniol, citronellol.
Geranium rose oil.	<i>Pelargonium odorat</i> .	Geraniol, citronellol.
Jasmine oil.	<i>Jasminum grandiflorum</i> .	Benzyl acetate, linalol, benzyl alcohol, linalyl acetate, methyl anthranilate, indole.

<i>Name.</i>	<i>Source.</i>	<i>Constituents.</i>
Lavender oil.	<i>Lavandula vera.</i>	<i>l</i> -Linalyl acetate, linalol (pinene, cineol).
Lemon oil.	<i>Citrus limonum.</i>	Limonene, phellandrene, citral, citronellal, geranyl acetate, linalol.
Lemon-grass oil.	<i>Andropogon citratus.</i>	Citral (citronellal, methylheptenone, geraniol).
Neroli oil.	<i>Citrus bigardia</i> (blossoms).	<i>l</i> -Linalol, linalyl acetate, geraniol, methyl anthranilate, limonene.
Orange oil.	<i>Citrus aurantium</i> (rind).	<i>d</i> -Limonene (citral, citronellal, methyl anthranilate).
Peppermint oil.	<i>Mentha piperita.</i>	Menthol and menthyl esters of acetic, valeric, and other acids, menthone (pinene, phellandrene, <i>l</i> -limonene, cineol, cadinene $C_{15}H_{24}$, acetic and iso-valeric aldehyde, methyl sulphide and anyl alcohol).
Pine-needle oil.	<i>Pinus sylvestris.</i>	<i>d</i> -Pinene, <i>d</i> -sylvestrene.
Rose oil.	<i>Rosa damascena.</i>	Geraniol, <i>l</i> -citronellol (geranyl acetate).
Rosemary oil.	<i>Rosamarinus officinalis.</i>	Pinene, camphene, cineol, camphor, borneol.
Sage oil.	<i>Salvia officinalis.</i>	Pinene, cineol, thujone, borneol.
Sassafras oil.	<i>Sassafras officinalis.</i>	Safrole (pinene, phellandrene, camphor, eugenol).
Spearmint oil.	<i>Mentha viridis.</i>	<i>l</i> -Linalol, <i>l</i> -carvone (cineol, <i>l</i> -limonene).
Star anise oil.	<i>Illicium anisatum.</i>	Anethole (<i>d</i> -pinene, <i>l</i> -phellandrene, estragol, quinol, ethyl ether, safrole).
Tansy oil.	<i>Tanacetum vulgare.</i>	Thujone (camphor, borneol).
Thyme oil.	<i>Thymus vulgaris.</i>	Thymol or carvacrol (cymene, <i>l</i> -pinene, borneol, linalol).
Wormwood oil.	<i>Artemisia absinthum.</i>	Thujone, thujyl alcohol, free and combined with acetic, isovaleric, and palmitic acids, phellandrene and cadinene.
Ylang-ylang oil.	<i>Cananga odorata</i> (flowers).	<i>l</i> -Linalol, geraniol, benzoic ester, <i>p</i> -cresol, methyl ether, cadinene.

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CHAPTER XIV

THE ALKALOIDS

AMONG vegetable products numerous oily and crystalline basic substances termed *alkaloids* have been found, which, in consequence of very marked physiological properties, have been objects of special interest to the chemist and physiologist. The first of these substances to be isolated was a crystalline compound obtained from opium by Derosne in 1808, and called by him *opium salt*, but he failed to recognize its basic character. In 1806 Sertürner, a German apothecary of Eimbeck, independently discovered the same crystalline substance, which he called *morphium* and pointed out its alkaline nature. At the same time he separated an acid which he called *meconic acid*, and expressed the view that the two substances existed in opium in combination. This investigation remained unnoticed at the time; but a second paper published by him in 1817, 'Ueber das Morphium, eine neue salzfähige Grundlage und die Mekonsäure als Hauptbestandtheile des Opiums,' attracted the attention of chemists, who thereupon began to search among vegetable products for similar substances. Success attended their efforts. In the same year Robiquet found narcotine in opium; in 1818 Pelletier and Caventou obtained strychnine from *nux vomica*; in the following year they separated brucine, and in 1820 they prepared quinine and cinchonine from cinchona bark. Since then scarcely a year has passed without the discovery of one or more alkaloids. At the present time the number exceeds two hundred, and the field is not exhausted.

These vegetable bases, all of which contain nitrogen, were regarded as conjugated ammonias by Berzelius (p. 33), and as substituted ammonias by Liebig and Hofmann, the latter recognizing the majority of them as tertiary bases. Numerous attempts to carry the investigation of these compounds further, and to explain their structure, proved unsuccessful, until it was discovered that certain basic oils, found by Anderson in bone-oil and by Runge and Greville Williams in coal-tar, were identical with the compounds obtained by Gerhardt by distilling some of the alkaloids with caustic potash. The sequence of events was as follows: In 1884 Runge separated the

substance which he termed *leucole* from coal-tar; in 1846 Anderson isolated pyridine and its homologues from bone-oil. Meanwhile Gerhardt (1842) had been subjecting strychnine, cinchonine, and quinine to distillation with solid caustic potash, and obtained an oil which he called quinoline, afterwards altered to quinine. Hofmann soon recognized in Runge's *leucole* and Gerhardt's quinoline identical substances. Subsequently other alkaloids—nicotine, conine, piperine, &c.—were converted into pyridine or one of its derivatives by heating with zinc dust. Isoquinoline, which was discovered in coal-tar in 1885 by Hoogewerff and van Dorp, has been shown to be related in a similar way to hydrastine, papaverine, narcotine, and berberine.

These discoveries, whilst they gave a fresh stimulus to the investigation of the alkaloids, opened up a new field for research in the study of pyridine and quinoline derivatives. The result has been that the process of graduated disintegration applied to the alkaloids on the one hand, and the construction of new products from pyridine and quinoline on the other, established points of contact between them which gradually disclosed the structure of many of the alkaloids, and ultimately led to the synthesis of a few of them.

The history of these successive stages is the main object of the present chapter. In the light of this new knowledge, how is the term alkaloid to be defined? Koenigs suggested that the name, which was originally applied to all vegetable bases, including caffeine, theobromine, betaine, choline, &c., should be restricted to those vegetable products which are derivatives of pyridine only. This would exclude caffeine and theobromine, which do not differ very widely from the alkaloidal bases. In the present state of the subject an exact definition is not easy to frame, and possibly, as our knowledge grows, the line of demarcation between the alkaloids at present known and other vegetable products may become gradually obliterated. For the present, however, an alkaloid may be defined as a vegetable base which contains a cyclic nitrogenous nucleus.

Before passing to the more complex alkaloids, a brief review of the parent substances seems desirable, and we propose, therefore, to describe briefly the properties and structure of pyridine, quinoline, and isoquinoline, and their more important derivatives, before passing to the chemistry of the alkaloids. It would be beyond the scope of these essays to attempt more than a general description of these substances, the number being already vast enough to have filled a volume of respectable dimensions.¹

¹ See References at the end of the chapter.

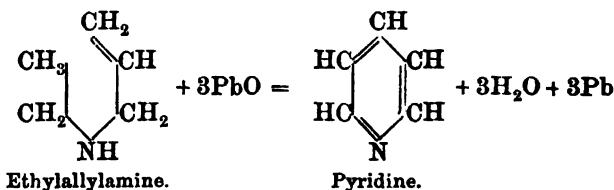
Pyridine. It has already been stated that pyridine and its homologues were first obtained by Anderson from bone-oil. This oil which is formed by the destructive distillation of bones, contains a large number of compounds derived from the decomposition of the albuminoid material of the bone. The bases are extracted from the distillate with acid, liberated by the addition of alkali and finally fractionated. The chief source of pyridine at present is coal-tar-naphtha, from which it is separated by sulphuric acid employed in purifying the naphtha. It is also formed by the action of alkalis or zinc dust at a high temperature on several of the alkaloids—nicotine, morphine, cinchonine, &c.—by the oxidation of piperidine (hexahydropyridine, see p. 559) with strong sulphuric acid at 300° or nitrobenzene at 250°, and by distilling the lime salts of pyridine carboxylic acids with lime. It has, moreover, been obtained synthetically by the following methods, all of which, it may be added, give unsatisfactory yields. This is not the case with the reactions to be described later for the preparation of certain pyridine derivatives.

In 1877 Ramsay,¹ following the lines of Berthelot's synthesis of benzene from acetylene, passed a mixture of acetylene and hydrocyanic acid through a red-hot tube and obtained small quantities of pyridine.



Koenigs² in 1879 was successful in obtaining some pyridine by distilling ethylallylamine over hot litharge.

Using the generally accepted formula for pyridine (it is discussed later, p. 551), the following represents the reaction :

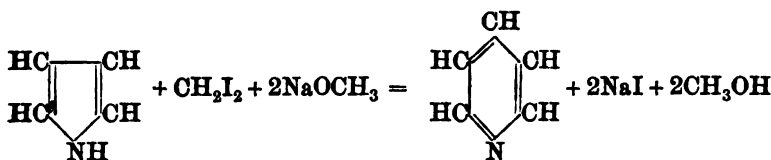


In 1885 Dennstedt and Zimmermann³ acted upon pyrrole and sodium methylate at 200° (or pyrrole potassium) with methylene iodide. The action is a curious one, and can only be formulated by supposing the pyrrole ring to open and absorb an additional carbon group.

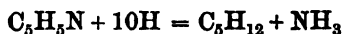
¹ Ber., 1877, 10, 786.

² Ber., 1879, 12, 2844

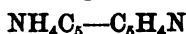
³ Ber., 1885, 18, 8316.



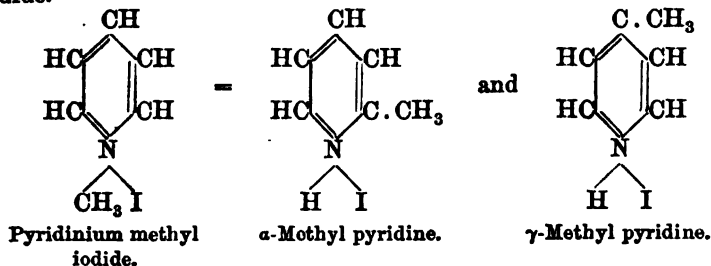
Pyridine is a colourless liquid, possessing a peculiar smell. It boils at 114.8° , and has nearly the same specific gravity as water. It is easily soluble in water as well as in most of the common solvents, and forms crystalline salts and double salts like other organic bases. It is peculiarly stable towards oxidising agents, chromic and strong or weak nitric acid having little or no action. The halogens also react with difficulty, so that the halogen derivatives, as well as amino compounds, are usually prepared by indirect methods, which will be described later. Strong or fuming sulphuric acid has little action at ordinary temperatures, but a sulphonc acid can be obtained by heating pyridine with the fuming acid at 300° . By the action of sodium on an alcoholic solution of pyridine, hexahydropyridine (piperidine) is obtained, whereas hydriodic acid at a high temperature decomposes it into normal pentane and ammonia.



Sodium alone removes an atom of hydrogen from pyridine, and dipyridyl is formed by the linking of two molecules,

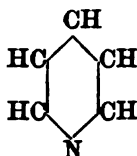


Pyridine is a tertiary base, and therefore forms quaternary compounds with the alkyl halides. These bodies undergo molecular change on heating to 300° , resembling the decomposition of the hydrochlorides of the monoalkyl anilines. Just as *o*- and *p*-toluidine are produced by heating methylaniline hydrochloride under pressure (p. 215), so α - and γ -methyl pyridine are obtained from pyridinium methyl iodide.

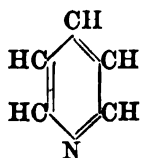


This reaction has furnished a number of important homologues of pyridine.

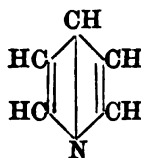
The great stability of pyridine, its analogy in chemical behaviour with benzene, the formation of a hexahydride, and the existence of three mono-substitution derivatives point to the structure of pyridine as a ring of six atoms, of which five are carbon and one is nitrogen. Each of the carbon atoms being united to one atom of hydrogen,



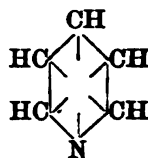
there remain six single valencies which have been accounted for by the use of different formulae. Körner in 1869 first suggested the application of Kekulé's formula to pyridine; this was followed by the formula of Riedel in 1883 and of Bamberger in 1891.



Körner.



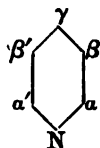
Riedel.



Bamberger.

There are arguments which may be adduced in favour of all three formulae; but the experimental data are at present too incomplete to afford a final decision. As the constitution of pyridine is closely interwoven with that of quinoline, we have deferred its discussion to the end of the present section (p. 551). In the meantime we shall adopt the Körner formula.

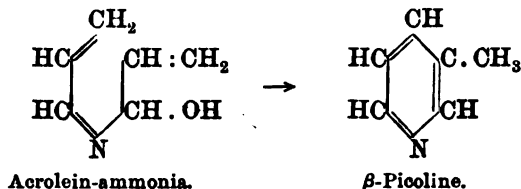
The substitution products of pyridine are denoted by the Greek letters α , β , γ or by numbers.



All three methyl and ethyl pyridines, hydroxy-, chloro-, and amino-pyridines and pyridine carboxylic acids are known.

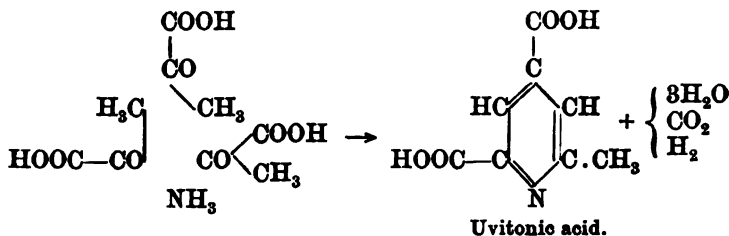
The alkyl pyridines resemble pyridine in most of their chemical properties, and, like the homologues of benzene, the side-chains are oxidisable, and acids result. The origin of some of these compounds has already been mentioned. All three methyl pyridines or picolines

are present in bone-oil. Baeyer¹ found that the resin obtained by the action of ammonia upon acrolein yields on distillation β -picoline. The constitution of acrolein-ammonia is not definitely known, but the formula and its transformation into picoline may probably be represented as follows:

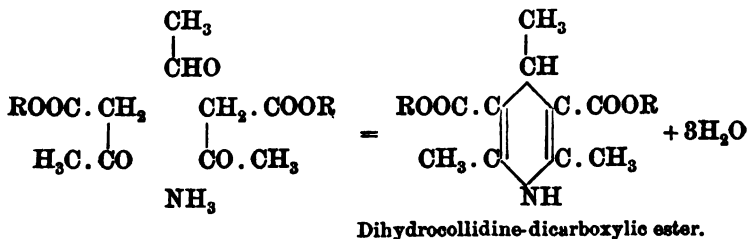


This method was the forerunner of others in which aldehyde-ammonias with or without the addition of an aldehyde or ketone were employed. We select two examples, the formation of α -picoline by Böttinger² and that of collidine (*s*-trimethylpyridine) by Hantzsch.³

By the action of ammonia on pyruvic acid a dibasic acid, uvitonic acid $\text{C}_6\text{H}_5\text{N}(\text{COOH})_2$, is formed, which, on distillation with lime, loses carbon dioxide and yields α -picoline.



By heating together gently for a few minutes two equivalents of acetoacetic ester with one of acetaldehyde-ammonia, dihydrocollidine-dicarboxylic ester results.



¹ *Annalen*, 1870, 155, 281.

² *Ber.*, 1877, 10, 362; 1880, 13, 2082.

³ *Ber.*, 1883, 15, 2914.

This compound, on oxidation with nitrous acid, loses two atoms of hydrogen, forming collidine-carboxylic ester, from which, on hydrolysis and distillation with lime, collidine is obtained.

Special interest attaches to those alkyl pyridines which are derived from the alkaloids themselves. By distilling conine hydrochloride with zinc dust, Hofmann obtained a base boiling at 166–168°, which he termed *conyrrine*, and which has since been identified as α -propyl pyridine.

Nicotine passed through a red-hot tube yields β -ethyl pyridine and β -propyl pyridine, whereas the hydrochloride of norhydrotropidine, a decomposition product of atropine, gives on distillation with zinc dust α -ethyl pyridine. Williams obtained β -ethyl pyridine by distilling cinchonine and quinine with caustic potash. Instances of the same thing might be multiplied.

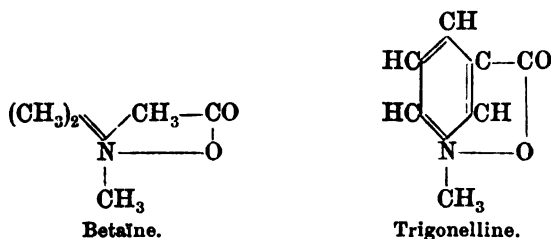
The pyridine carboxylic acids have also played an important part in fixing the structure of the alkaloids. As the degradation of the alkaloids by oxidation generally results in the production of one or other of these acids, it has been a matter of the first importance to determine the position of the carboxyl groups in the pyridine nucleus. This has been satisfactorily accomplished by methods for a description of which the reader is referred to one of the larger textbooks. The methods of preparation are the same as those used in the case of the acids of benzene, namely, the oxidation of side-chains or the hydrolysis of the nitriles.

The following acids have a special interest, arising from their direct or indirect connection with the alkaloids: *Nicotinic acid* (β -pyridine carboxylic acid) is obtained from nicotine, pilocarpine, hydrastine, and berberine by oxidation and by the action of hydrochloric acid on trigonelline (see below); the following are also obtained by oxidation: *quinolinic acid* (α - β -pyridine dicarboxylic acid) from quinoline; *cinchomeronic acid* (β - γ -pyridine dicarboxylic acid) from isoquinoline, *α -carbocinchomeronic acid* (α - β - γ -pyridine tricarboxylic acid) from several of the cinchona alkaloids, and papaverine and berberonic acid (β - γ - α' -pyridine tricarboxylic acid) from berberine.

The α -carboxylic acids occupy a distinctive position among the pyridine acids, owing to the facility with which they lose carbon dioxide on heating, and also by reason of the yellow colour reaction which they give with ferrous sulphate. Although the pyridine acids naturally possess basic as well as acid characters, the usual reactions of the carboxyl group are not thereby affected. From the acids the corresponding amide and, by means of Hofmann's hypobromite

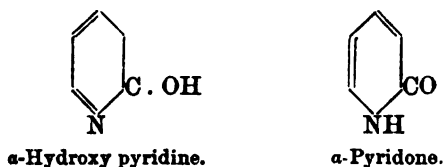
reaction, the amino pyridines may be prepared. The latter resemble the aliphatic amines rather than the aromatic amino compounds; for only the β -compound can be diazotised with nitrous acid, and manifests the usual reactions of diazo compounds.

It has been stated that trigonelline is converted into nicotinic acid by the action of hydrochloric acid. This alkaloid, which is found in fenugreek (*trigonella foenum-graecum*), represents a new and interesting class of compound now recognized by the generic term of *betaines*. Betaine has long been known as a constituent of beetroot sap, and its constitution has been fixed by synthesis as the inner anhydride of hydroxytrimethylglycocoll. In 1885, Jahns¹ discovered trigonelline in the seeds of fenugreek, and showed that the substance was identical with a compound obtained by Hantzsch from nicotinic acid, by treating the acid successively with methyl iodide and silver hydroxide. The relationship between these two substances is readily understood from the following formulae:



Similar compounds have been found among the oxidation products of cotarnine and hydrastinine.

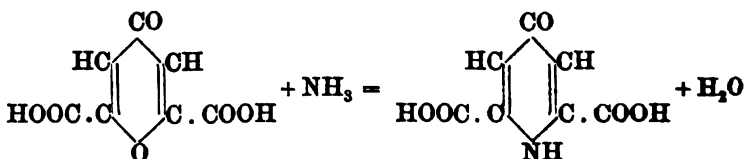
The only other group of compounds to which reference need be made are the hydroxy pyridines. These substances possess both basic and phenolic properties and correspond to the amino phenols. The α - and γ -compound, but not the β -compounds, are also characterized by their behaviour as ketones or lactams, in other words, they exhibit the property of tautomerism, and may therefore be represented by the following double formulae:



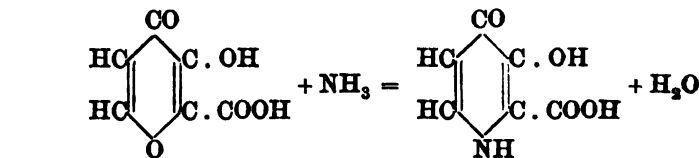
¹ Ber., 1885, 18, 2518.

 γ -Hydroxy pyridine. γ -Pyridone.

They are usually obtained by removing carboxyl from the hydroxypyridine carboxylic acids by distillation with lime. The α - and γ compounds may also be prepared from the derivatives of α - and γ pyrones by the action of ammonia in the cold, the single oxygen atom being replaced by the NH group. This connection between the pyrones and hydroxypyridines is a peculiarly interesting one, since pyrone compounds, associated with alkaloids, are widely distributed among plants. Thus, Lieben and Haitinger¹ found that chelidonic acid, which occurs with the alkaloid chelidonine in the root of common celandine, is converted into chelidamic or γ pyridone dicarboxylic acid.

Chelidonic acid
(γ -Pyrone dicarboxylic acid).Chelidamic acid
(γ -Pyridone dicarboxylic acid).

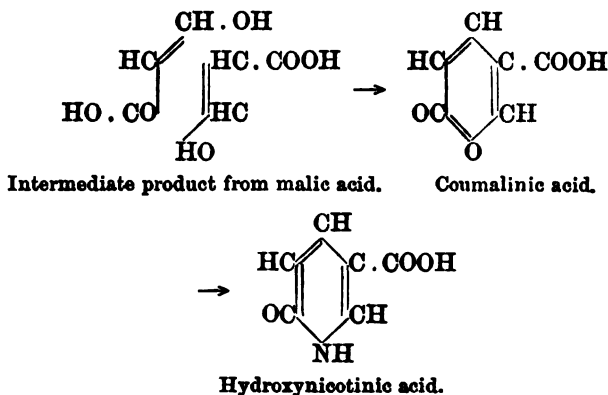
Ost² obtained in the same way from comenic acid (hydroxy- γ pyrone carboxylic acid), which is formed by heating meconic acid of opium, comenamic acid, or dihydroxypicolinic acid.

Comenic acid
(β -Hydroxypyryrone carboxylic acid).Comenamic acid
(Dihydroxypicolinic acid).

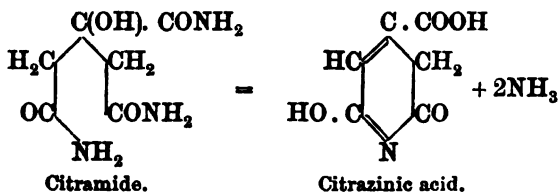
Another interesting synthesis of the same character is the formation of hydroxynicotinic acid from coumalinic acid.³ Coumalinic acid is obtained by the action of strong sulphuric acid on malic acid,

¹ *Monatsh.*, 1883, 4, 275; 1885, 6, 279.² *J. prakt. Chem.*, 1883, 27, 257; 1884, 29, 57, 378.³ Von Pechmann and Welsh, *Ber.*, 1884, 17, 986, 2384; 1885, 18, 317.

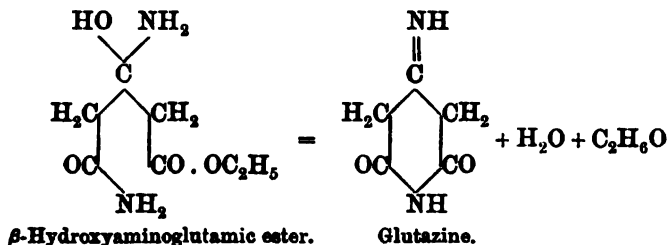
in which the intermediate formation of hydroxymethylene acetic acid may be assumed to occur.



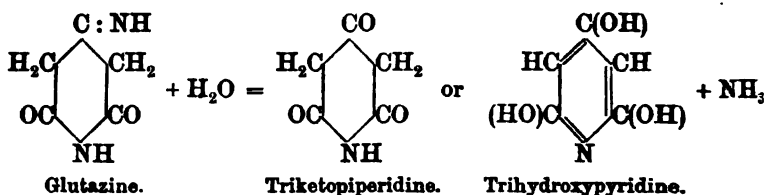
If, as seems on the whole not improbable, the pyrones form the basis of some of the alkaloids, a simple mode of preparing pyrone compounds may throw some light on the initial stages of the synthetic process by which these complex molecules are elaborated in the plant. Di- and tri-hydroxypyridines and hydroxypyridine carboxylic acids have also been obtained indirectly from citric acid. Thus, hydrochloric acid converts citramide or one of the amides of citric acid into citrazinic acid (*aa'*-dihydroxynicotinic acid).



Glutazine (*aa'*-dihydroxy- γ -amino pyridine) is obtained by the acting on acetonedicarboxylic ester with ammonia and boiling the product, β -hydroxyaminoglutamic ester, with soda solution.



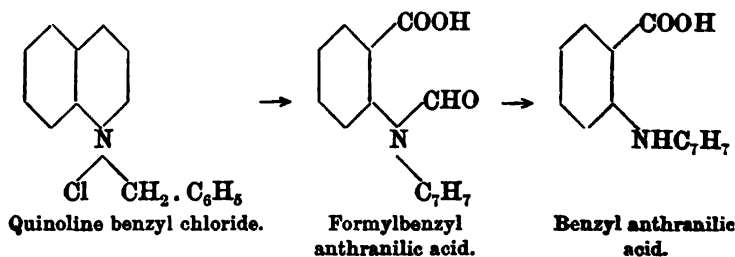
By boiling glutazine with hydrochloric acid, triketopiperidine or $\alpha\alpha'\gamma$ -trihydroxypyridine is produced.



As acetonedicarboxylic ester is a product of the action of sulphuric acid on citric acid, both this and the previous product may be regarded as indirectly obtained from citric acid.

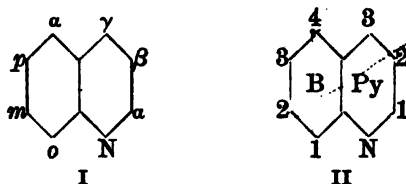
Quinoline. In chemical properties quinoline offers many points of resemblance to pyridine. It is a colourless, oily liquid, specifically heavier than water, in which, unlike pyridine, it is only slightly soluble. It boils at 240° . On reduction it takes up 4, 8, and finally 10 additional atoms of hydrogen, forming decahydroquinoline.

Quinoline bears very much the same relation to pyridine that naphthalene does to benzene. Thus, on oxidation with permanganate solution, quinolinic acid, i. e. $\alpha\beta$ -pyridine dicarboxylic acid, is formed, whereas the additive product of quinoline with benzyl chloride gives under similar conditions a mixture of the benzyl derivatives of anthranilic acid and formyl anthranilic acid.



It seems as if the ring containing nitrogen in its quinquivalent state were rendered less resistant to oxidising agents.

The appearance of a pyridine nucleus in the product of the first process and of a benzene nucleus in that of the second has led to the hypothesis of a double hexagon formula for quinoline, consisting of a benzene and pyridine ring having two carbon atoms common to both.

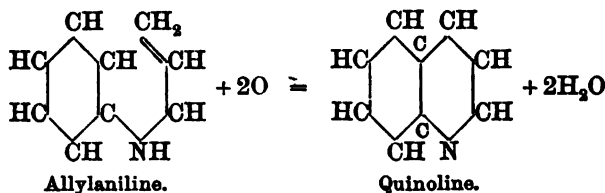


This arrangement of the atoms would also agree perfectly well with the various syntheses of quinoline and its derivatives described below; but a fuller discussion of the subject is reserved for the conclusion of the section (p. 551).

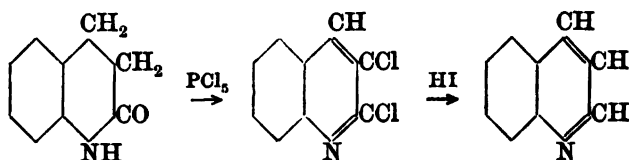
The seven hydrogen atoms, according to the hexagon formula, are evenly distributed among the carbon atoms, which are distinguished by the Greek letters α , β , γ in the pyridine nucleus, and by ortho, meta, para, and ana in the benzene ring (I), or, according to another method, by numbers following the initial letters B or Py, to indicate the benzene or pyridine nucleus respectively (II). Seven mono derivatives of quinoline are therefore possible, and of these all the methyl quinolines and quinoline carboxylic acids, and six of the seven hydroxyquinolines, are known.

Quinoline and some of its homologues are obtained from coal-tar, from certain alkaloids by distillation with potash, or by means of one or other of numerous synthetic methods from which the following are selected :

In 1879 Koenigs¹ obtained quinoline, in a similar manner to that by which he prepared pyridine, by passing the vapour of allylaniline over heated lead oxide.

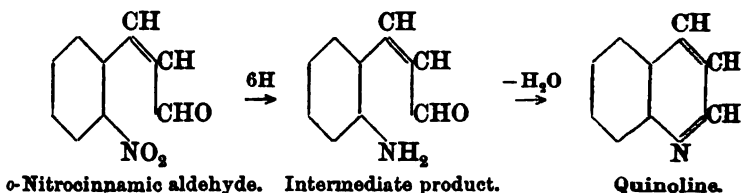


In the same year Baeyer converted hydrocarbostyryl (the anhydride of *o*-aminohydrocinnamic acid) into quinoline by the successive action of phosphorus pentachloride and hydriodic acid.

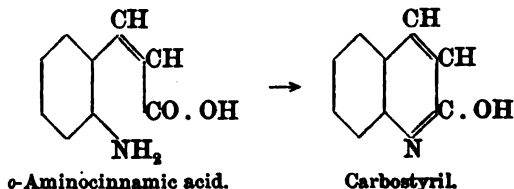
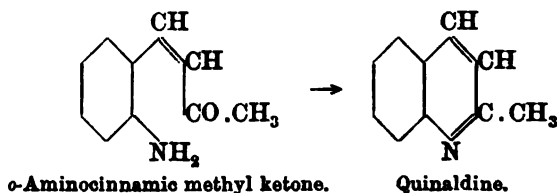


¹ Ber., 1879, 12, 458.

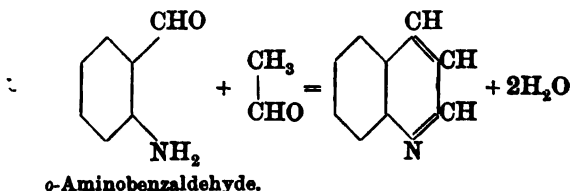
This method was afterwards modified,¹ and in place of aminocinnamic acid, *o*-nitrocinnamic aldehyde was reduced.



To the same category of reactions belong the formation of quinaldine (α -methyl quinoline) from *o*-aminocinnamic ketone and carbostyryl (α -hydroxyquinoline) from *o*-aminocinnamic acid.



A further interesting development of the method is due to Friedländer, who in 1888² obtained quinoline by condensing *o*-aminobenzaldehyde with acetaldehyde in presence of a little caustic soda solution.

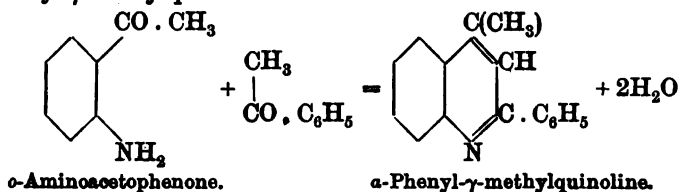


In place of acetaldehyde, a variety of aldehydes and ketones may be used, and even the aldehyde group of the basic constituent may be replaced by a ketone.

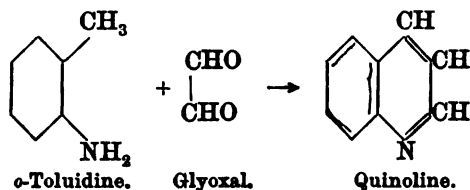
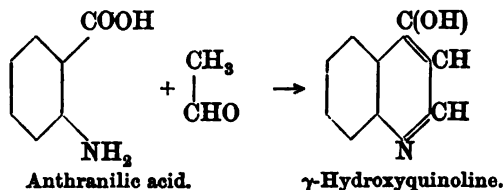
¹ Ber., 1883, 16, 2307.

² Ber., 1882, 15, 2572; 1883, 16, 1833.

To take one example, *o*-aminoacetophenone gives with acetophenone, α -phenyl- γ -methylquinoline.

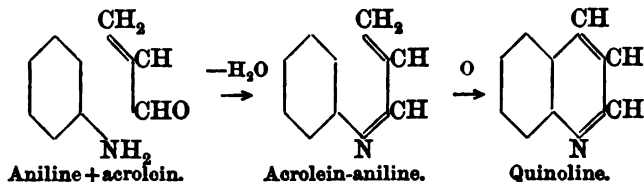


Anthranilic acid and *o*-toluidine have also been used in conjunction with aldehydes for effecting quinoline synthesis.



To a somewhat different class of reactions belongs the important synthetic method of Skraup.

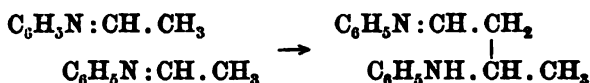
In 1880 Koenigs obtained quinoline by heating nitrobenzene with glycerol and sulphuric acid at $180\text{--}190^\circ$, a reaction which was very soon replaced by the more effective process of Skraup,¹ which appeared in the same year. It consists in heating an aromatic amino compound with glycerol, sulphuric acid, and nitrobenzene. The mechanism of Skraup's method is usually explained by assuming that glycerol undergoes conversion into acrolein by the dehydrating action of the acid, and is followed by the formation of acrolein-aniline with the aniline or aniline derivative. This acrolein-aniline is then oxidised by the nitrobenzene to quinoline.



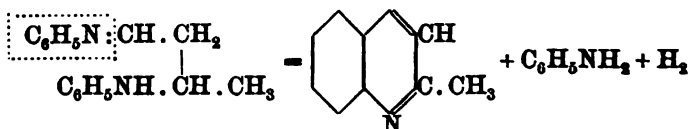
¹ *Monatsh.*, 1880, 1, 816; 1881, 2, 141.

The method is of the greatest value, for, provided one ortho position to the amino group in the nucleus is free, any amino compound may be used, and the number of substituted quinolines which can be prepared in this way is very large. The substituent group in these cases is naturally restricted to the benzene nucleus.

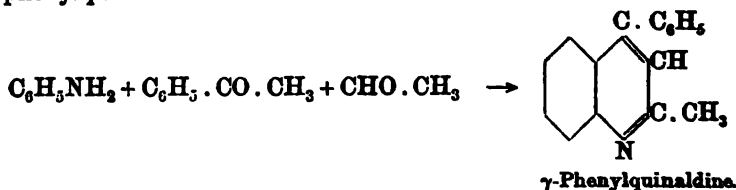
The quinaldine synthesis of Doebner and von Miller must complete this brief summary of synthetic methods. It consists in the action of sulphuric or hydrochloric acid upon a mixture of aniline and aldehydes. From aniline and acetaldehyde (or paraldehyde) α -methylquinoline or quinaldine is obtained. The mechanism of the process probably consists in the condensation of two molecules of alkylidene aniline (formed by union of the aldehyde and aniline), thus:



It is followed by the elimination of aniline and hydrogen with ring formation.



In place of aldehyde or ketone, mixtures of aldehydes and ketones may be used. With aniline, acetophenone, and acetaldehyde, γ -phenylquinaldine has been obtained.



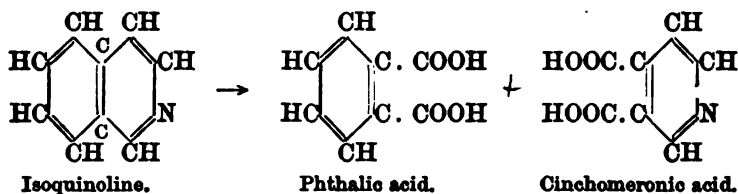
An adequate account of the chemistry of quinoline and its derivatives would carry us far beyond the scope of the present essay, which is intended to include only those compounds possessing some kind of relation to the alkaloids.

Numerous alkyl quinolines have been prepared synthetically by one of the methods already described and possess the general characteristics of quinoline. Lepidine or γ -methylquinoline can be obtained from cinchonine by distillation with potassium hydroxide or lead oxide, and it is also interesting to note that *p*-methoxylepidine occurs among the decomposition products of quinine. γ -Phenylquinoline is another product which brings us into touch with the

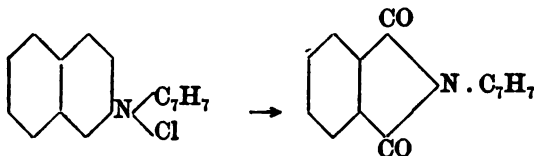
alkaloids, for, according to Koenigs, it is the parent substance of quinine.

The following quinoline acids are also directly related to the alkaloids: *cinchoninic acid* (γ -quinoline monocarboxylic acid) is obtained by oxidising several of the cinchona alkaloids, and *quininic acid* (*p*-methoxycinchoninic acid) is formed by the oxidation of quinine.

Isoquinoline, which is isomeric with quinoline, is a colourless solid, melting at 21° , boiling at 240° , and possessing a smell like quinoline. It was originally found by Hoogewerff and van Dorp¹ in coal-tar in the crude quinoline fraction and separated by crystallization of the slightly soluble sulphate. On oxidation it gives both phthalic and cinchomeronic acid, which points to the following structural formula:



Also alkyl isoquinolinium halides give on oxidation alkyl phthalimides.



This structure has been confirmed by subsequent synthesis, which was first accomplished in 1886 by Gabriel. Homophthalimide is converted by phosphorus pentachloride into dichloroisoquinoline, which on further heating with hydriodic acid and phosphorus passes into isoquinoline, identical with Hoogewerff and van Dorp's base.

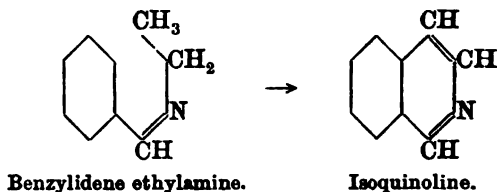


Le Blanc² has effected the same result more directly by heating homophthalimide with zinc dust in a current of hydrogen. A

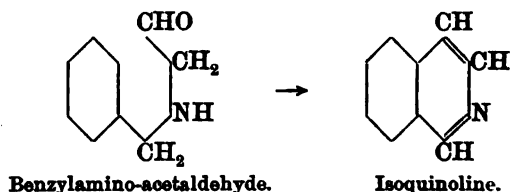
¹ *Rec. trav. chim.*, 1885, 4, 125.

² *Ber.*, 1888, 21, 2299.

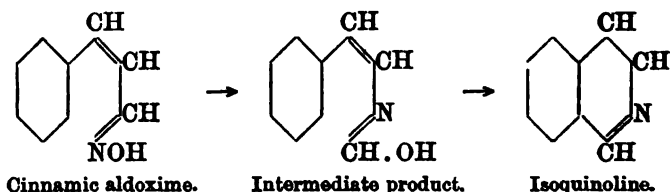
reaction, resembling the formation of quinoline from allylaniline, which consists in passing benzylidene ethylamine through a red-hot tube, also furnishes isoquinoline.



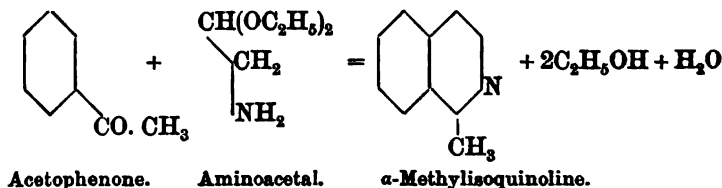
Fischer¹ obtained isoquinoline by dissolving benzylamino-acetaldehyde in fuming sulphuric acid, which acts both as a dehydrating and oxidising agent.



An interesting isoquinoline synthesis was effected by Bamberger and Goldschmidt,² who found that both stereoisomers of cinnamic aldoxime on distillation with phosphorus pentoxide undergo the Beckmann change and give isoquinoline as follows (p. 218):



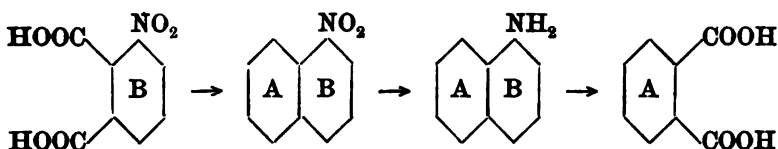
Pomeranz obtained α -methylisoquinoline by the action of strong sulphuric acid on a mixture of aminoacetal and acetophenone.



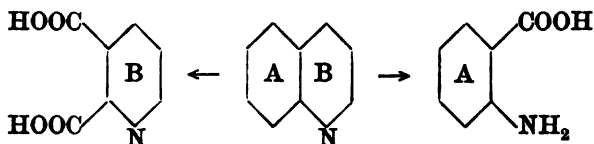
¹ Ber., 1898, 26, 764.

² Ber., 1894, 27, 1954, 2795.

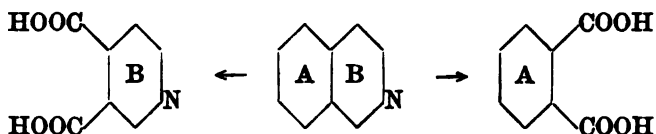
Structure of Pyridine, Quinoline, and Isoquinoline. In discussing in further detail the constitution of pyridine, quinoline, and isoquinoline, that of naphthalene may be included, since the same process of reasoning has been applied in turn to each. Assuming that benzene and pyridine form rings of six atoms, it follows that quinoline, isoquinoline, and naphthalene are each composed of a double nucleus of six atoms, two of which are common to both nuclei. For, in the case of naphthalene, it has been shown that if either nucleus is removed by oxidation a benzene derivative results. Graebe found that if α -nitronaphthalene is oxidised, nitrophthalic acid is formed, whereas α -naphthylamine, obtained from the same α -nitronaphthalene by reduction, yields phthalic acid.



In the one case nucleus A is removed, in the other nucleus B, and in both cases a benzene nucleus remains. Quinoline in the same way may be oxidised to quinolinic acid on the one hand, and to a derivative of anthranilic acid on the other (p. 544).



Under similar conditions isoquinoline gives a mixture of phthalic and cinchomeronic acid (p. 549).

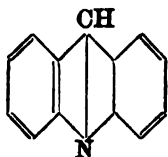


The symmetrical grouping of the hydrogen atoms is borne out by the existence of two isomeric mono derivatives of naphthalene, three of pyridine and seven of quinoline, whereas the equivalence of the two nuclei in the case of naphthalene follows from the fact that 2.7-dihydroxynaphthalene forms with alcohol and sulphuric acid a dialkyl ether. For this property of forming ethers after the manner of alcohols is not shared by the phenols of benzene, and, as

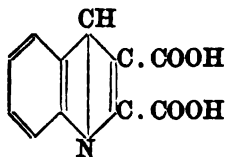
first pointed out by Bamberger, the formation of such an ether in both nuclei of naphthalene is strong evidence in favour of their symmetry.

Having set forth the facts upon which a symmetrical bi-cyclic nucleus is based, the issue narrows itself down to a discussion of the fate of the fourth carbon and third nitrogen bond. As in the case of benzene we have a choice of formulae, firstly, those modelled on Kekulé's formula for benzene, which include Erlenmeyer's naphthalene formula and Körner's formula for pyridine and quinoline, secondly, those modelled on the Armstrong and Baeyer centric formula, which is represented by Bamberger's formula for naphthalene, quinoline, and isoquinoline, and finally Riedel's diagonal formula for pyridine and quinoline.

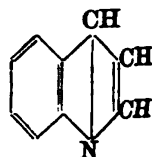
Riedel's formula¹ may be dismissed in a few words. It rests mainly upon the formation of acridinic acid (quinoline dicarboxylic acid) from acridine by oxidation, and certain synthetic methods involving the use of aliphatic compounds. As acridine, like anthracene, is supposed to possess a para linkage connecting the nitrogen and carbon of the middle nucleus, the same kind of linkage is retained in the quinoline and also in the pyridine formula.



Acridine.



Acridinic acid.



Quinoline.

Such an assumption, quite apart from the uncertainty which surrounds the structure of acridine itself, implies an immobility of the para linkage during the degradation of the molecule which does not necessarily follow. The formula is moreover difficult to reconcile with the mechanism of those synthetic methods by which the majority of pyridine and quinoline derivatives are prepared.

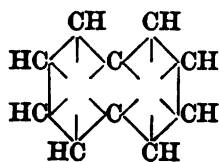
None of these difficulties are presented by either the Kekulé or centric type of formula. At the same time it must be admitted that the Kekulé type of formula is open to precisely the same kind of criticism which benzene affords, and which has been fully discussed on p. 445.

But suppose we accept Kekulé's formula for benzene and pyridine, does the formation of benzene derivatives from naphthalene, and

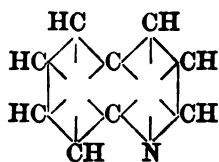
¹ Ber., 1888, 16, 1609.

both benzene and pyridine derivatives from quinoline and isoquinoline, necessarily imply the pre-existence of these nuclei in the original compound?

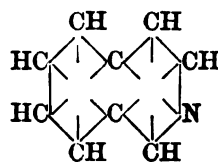
Although at first sight an affirmative reply to the question appears the most simple and obvious one, Bamberger¹ has shown that there are many experimental facts which are opposed to it, and he prefers to regard all three compounds as represented by a ring of ten atoms, in which the fourth carbon, or third nitrogen, bond, as the case may be, are directed towards the centre of each nucleus thus:



Naphthalene.



Quinoline.

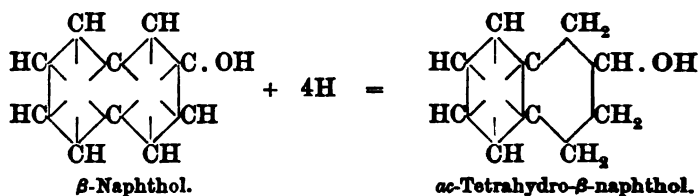
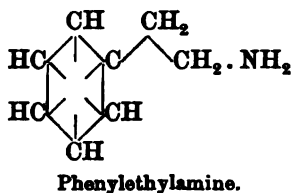
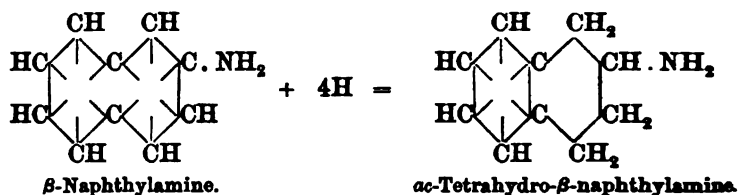


Isoquinoline.

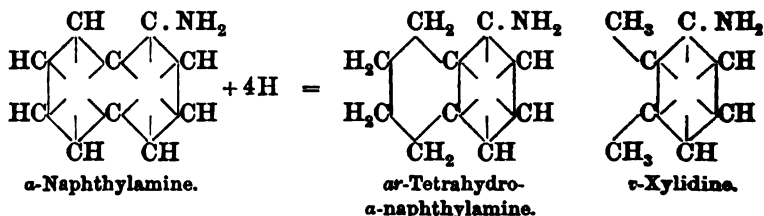
The evidence in favour of this theory will now be briefly reviewed. By the action of sodium in amyl alcohol solution upon α - and β -naphthol and α - and β -naphthylamine, Bamberger obtained tetrahydro compounds in which four atoms of hydrogen were added either to the substituted or unsubstituted nucleus. The two hydrogenated compounds, which are formed simultaneously, can be separated by suitable means and their nature determined by the products of oxidation. If the reduced nucleus contains the amino or hydroxyl group, the compound loses its aromatic character and takes that of an aliphatic compound. In this case the compound is termed alicyclic = *ac* (*ἄλειφαρ*, fat; *κύκλος*, ring), since it contains a closed chain having aliphatic properties. Thus, *ac*-tetrahydro- β -naphthylamine closely resembles phenylethylamine in ammoniacal smell, strongly basic character, and in the stability of its crystalline nitrite; further, in the fact that, by the action of dilute sulphuric acid and hydrobromic acid, ammonia is evolved, and in each case an unsaturated hydrocarbon (styrene in the one case and dihydronaphthalene in the other) results. The corresponding *ac*-tetrahydro- β -naphthol has the properties of an alcohol.

This is accounted for by supposing that in Bamberger's formula the withdrawal of the four free bonds of the substituted nucleus causes the two middle carbon atoms to unite, thereby converting the other nucleus into a benzene ring.

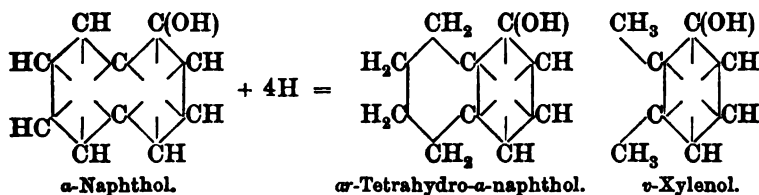
¹ *Annalen*, 1890, 257, 1.



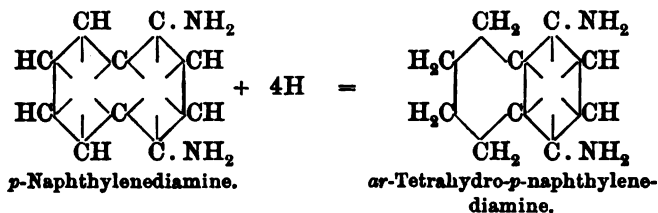
Suppose now that the unsubstituted nucleus has undergone reduction, the benzenoid character of the compound is accentuated, and to distinguish it from the other hydrogenated product it is termed aromatic = *ar*. Thus, *ar*-tetrahydro- α -naphthylamine is much more closely related to *v*-xylidine than to α -naphthylamine, for unlike the latter it gives no colour reaction with ethyl nitrite. On the other hand, it possesses the neutral reaction, the weak basic properties, and characteristic behaviour towards nitrous acid of an aromatic base. Here the withdrawal of the four bonds transforms the substituted nucleus into a benzene ring.



In the same way xyleneol resembles *ar*-tetrahydro- α -naphthol, for the latter, like all the phenols derived from benzene, is incapable of forming ethers with alcohol and sulphuric acid, whereas α - and β -naphthol in common with the alcohols possess this property.



Two more examples must suffice. Para-phenylenediamine can be readily converted into the colouring matters known as indamine, affranine, and thionine dyes. This property is entirely absent in the corresponding naphthalene derivative. If, however, *p*-naphthanediamine is reduced in the unsubstituted nucleus, the characteristic properties of the benzene derivative immediately appear. This is readily understood from the change of structure.



Again, the naphthoquinones combine with phenylhydrazine to form hydrazones, whilst quinones of the benzene series are merely reduced to the quinols. Hydrogenation in the unsubstituted nucleus produces tetrahydronaphthoquinones which show an exactly parallel behaviour with the benzoquinones and undergo reduction to tetrahydronaphthoquinols.

The results are embodied by Bamberger in the following three propositions:

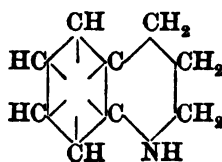
1. In naphthalene and in those derivatives in which each of the eight carbon atoms is linked to a univalent radical (or element) there exist two carbon systems, one of which becomes a benzene ring when the other takes up four atoms of hydrogen.

2. If one of the two carbon systems of naphthalene takes up four atoms of hydrogen, it assumes thereby the functions of an open aliphatic chain.

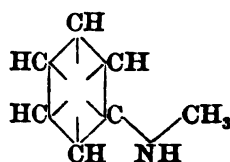
3. The process of hydrogenation of one system consists in converting the product into one resembling a benzene derivative with an aliphatic side-chain, the hydrogenated part assuming aliphatic, the non-hydrogenated part aromatic, functions.

The experience with naphthalene has been found by Bamberger to embrace other cyclic structures. If, for example, the pyridine

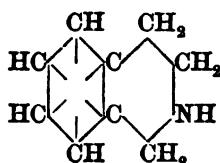
nucleus in quinoline and isoquinoline is reduced, the tetrahydro compounds so formed have the closest resemblance to methylaniline in the former case and to benzylamine in the latter.



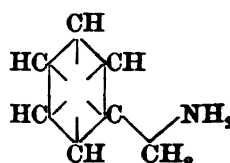
Tetrahydroquinoline.



Methylaniline.

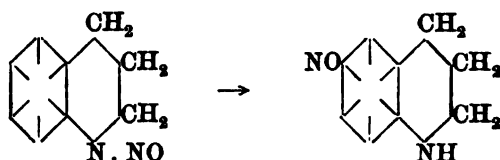


Tetrahydroisoquinoline.

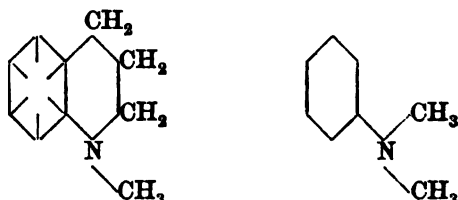


Benzylamine.

The resemblance is exhibited in the following way: Ziegler¹ showed that tetrahydroquinoline nitrosamine undergoes intramolecular change with alcoholic hydrogen chloride in precisely the same way as methylaniline nitrosamine; in both cases the nitroso group is transferred to the para position to the amino group (p. 217).



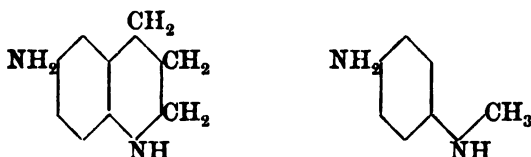
Again, the N-methyl derivative of tetrahydroquinoline behaves like dimethylaniline;



for it yields a *p*-nitroso derivative resembling nitrosodimethylaniline; it forms a corresponding leucomalachite green with benzaldehyde, which like that derived from dimethylaniline yields a green dye-stuff on oxidation, and it unites with diazonium salts to form red azo colours.

¹ Ber., 1888, 21, 862.

Moreover, *p*-aminotetrahydroquinoline gives the characteristic colour changes exhibited by an alkylated *p*-phenylenediamine, such as the



indamine and saffranine reactions when oxidised with aniline hydrochloride, toluylene red and blue colours with *m*-phenylenediamine, and methylene blue with hydrogen sulphide and ferric chloride.

Many other facts of a similar nature have been observed among derivatives of tri-cyclic systems.

General Properties of the Alkaloids. From the long list of vegetable bases a few typical and better-known examples have been selected, with the object of illustrating the manner in which the resolution of the alkaloid has been effected, the constituent fragments of the molecule identified, and the problem of its structure finally solved. It is impossible to lay down other than broad generalizations in describing the alkaloids. They are confined to no special orders or parts of plants; but they are specially abundant in the families of Rubiaceae, Solanaceae, and Papaveraceae, and rare in those of Labiatae and Rosaceae. It is seldom that only one alkaloid is present in the plant, more commonly there are several; in opium, for example, as many as twenty individuals have been isolated, and the alkaloids which are associated in this way are usually closely related in structure and properties. Where the alkaloids are of a strongly poisonous character they are probably elaborated by the protoplasm for defence against destruction by animals. A few, which like conine and nicotine are liquid, are as a rule free from oxygen, but the majority are solids and contain oxygen. The larger number of alkaloids are colourless, but a few, such as berberine and sinapine, have a yellow colour. They are very slightly soluble in water, but are much more readily dissolved by alcohol, ether, and other organic solvents. They possess a bitter taste, an alkaline reaction, and form crystalline salts and double salts. The majority are optically active and these are nearly all laevogyrate. They rarely exist in the plant in the free state, but are more frequently present as malates, citrates, lactates, tannates, or bound to some other acid which is a peculiar accompaniment of the alkaloid. Meconic acid, for example, is combined with morphine

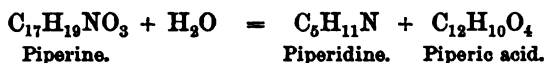
in opium, quinic acid with quinine, chelidonic acid with chelidone, and aconitic acid with the alkaloids of aconitine. The alkaloids contain one or two atoms of nitrogen, rarely three or four, and the nitrogen imparts to the compound the function of a secondary, or more frequently of a tertiary, base. The nitrogen is firmly fixed in the molecule; but it can be occasionally removed as ammonia by the action of strong reducing agents; by the action of alkalis it is sometimes eliminated as methylamine, indicating the attachment of methyl to the nitrogen in the molecule. The number of such methyl groups can be ascertained by a method analogous to that of Zeisel for estimating methoxyl groups. The stability of the cyclic nitrogen atom in the alkaloid is greatly weakened by making the element quinquevalent. An example of this character has been given in the case of the benzyl chloride compound of quinoline, which on oxidation gives a derivative of anthranilic acid. This property has been utilized by Hofmann in breaking down some of the alkaloids and will be referred to later. When oxygen is present in the alkaloid it is usually in the form of hydroxyl or methoxyl, and occasionally as carboxyl or an ester group. The ordinary methods can be applied in determining the number and nature of these groups. The chemical characters of the alkaloids are very diverse. Some, like piperine, are amides; others, like atropine, are esters; solanine is a glucoside. In all these cases they can be hydrolysed. Cocaine on hydrolysis splits up into methyl alcohol, benzoic acid, and a base, *ecgonine*. Where hydrolysis can be effected, it always precedes any other process of decomposition. The action of alkalis, of zinc dust and of other reducing agents, has been used to effect further changes, but, of all reactions, the most valuable results have usually been derived from regulated oxidation. Among the numerous oxidising agents, potassium permanganate in acid or alkaline solution, nitric and chromic acids are generally employed. The alkaloids are usually classified under (1) derivatives of pyridine; (2) derivatives of pyrrolidine; (3) derivatives of quinoline; (4) derivatives of isoquinoline; (5) derivatives of purine.

Examples are selected from each of these groups, excepting that of the purine bases, which is treated elsewhere (p. 867).

THE PYRIDINE ALKALOIDS

Piperine. The dried fruit of black pepper (*piper nigrum*) contains, in addition to a terpene and a resin, from 7-9 per cent. of a tasteless crystalline alkaloid termed piperine, which was discovered

in 1819 by Oersted. Its composition, $C_{17}H_{19}NO_3$, was first correctly ascertained by Regnault. Piperine is a weak base, and is without action on polarized light. In 1845 Wertheim and Rochleder¹ found that, on distilling it with soda-lime, a volatile liquid passed into the receiver, possessing a strong ammoniacal smell and basic properties, which Cahours named *piperidine*, and gave it the formula $C_5H_{11}N$. A few years later Babo and Keller² discovered that piperine could be decomposed by means of alcoholic potash into piperidine and the potassium salt of a new acid, to which the name *piperic acid* was given. The decomposition may be represented as follows:

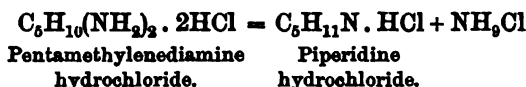


The result led to a partial synthesis by Rügheimer³ in 1882, by acting on piperidine with piperic chloride dissolved in benzene,



from which it follows that piperine is probably an amide. Piperidine has a powerful ammoniacal smell, a strongly alkaline reaction, and exhibits all the properties of a secondary base.

The first important contribution to our knowledge of the constitution of piperidine is due to Hofmann,⁴ who in 1879 showed that by heating it with bromine and water at 200–220°, dibromo-hydroxypyridine is formed. This close relationship to pyridine, from which piperidine differs by only six atoms of hydrogen, was further demonstrated by Koenigs⁵ in the same year, by converting it directly into pyridine by oxidation with strong sulphuric acid at 300°, and later by Lellmann and Geller, who used nitrobenzene at a temperature of 250°. Piperidine must therefore be regarded as hexahydropyridine, a conclusion which was supported by the subsequent reduction of pyridine to piperidine by means of tin and hydrochloric acid, or by sodium and alcohol. Its complete synthesis was effected by Ladenburg⁶ in 1885, by rapidly distilling the hydrochloride of pentamethylenediamine.



The latter compound is obtained from trimethylene bromide,

¹ *Annalen*, 1845, 54, 255.

² *Ber.*, 1882, 15, 1890.

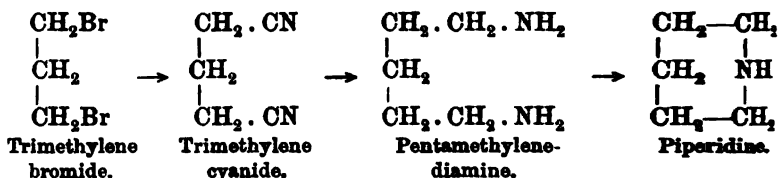
³ *Ber.*, 1879, 12, 2341.

⁴ *J. prakt. Chem.*, 1857, 72, 53.

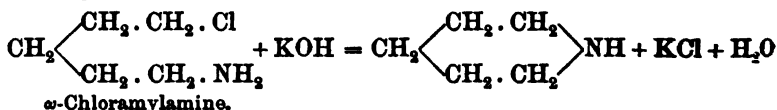
⁵ *Ber.*, 1879, 12, 985.

⁶ *Ber.*, 1885, 18, 2956, 3100.

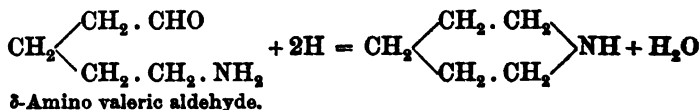
which is successively converted into trimethylene cyanide, and on reduction with sodium in alcoholic solution into pentamethylene diamine.



Other syntheses have since been discovered. Gabriel and Blank converted ω -chloramylamine and ω -bromamylamine into piperidine by treating with alkali,¹



and δ -amino valeric aldehyde, which is obtained by the oxidation of benzoyl piperidine, can by the reverse process of reduction be transformed into piperidine,



It may be well to consider here some of the changes produced by the action of certain reagents on piperidine and its derivatives, since similar reactions have been employed in the study of other alkaloids.

It has already been stated that when the nitrogen of the base becomes quinquivalent it is more subject to change. This was shown years ago by Hofmann² in the case of quaternary ammonium bases. Thus, tetraethylammonium hydroxide on heating breaks up into triethylamine, ethylene, and water.

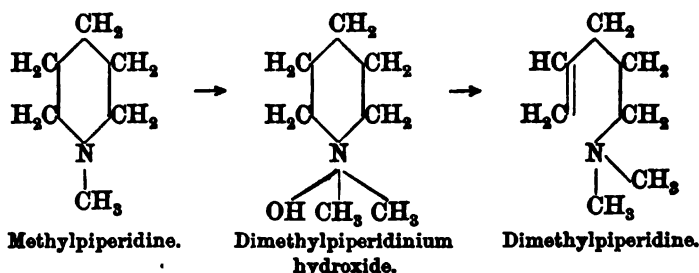


In applying this reaction to piperidine, a similar change occurs.¹ Piperidine is convertible into the tertiary base, methyl piperidine, by the action of methyl iodide, and forms an additive compound with methyl iodide which yields in the ordinary way dimethylpiperidinium hydroxide. The latter, on distillation, loses water and forms a compound having the composition of dimethyl piperidine. These changes have been shown by Ladenburg to occur in the following way:

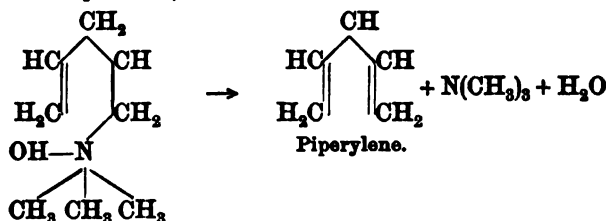
¹ Ber., 1892, 25, 421, 3040.

² Annalen, 1851, 78, 263.

³ Ber., 1881, 14, 494, 659.

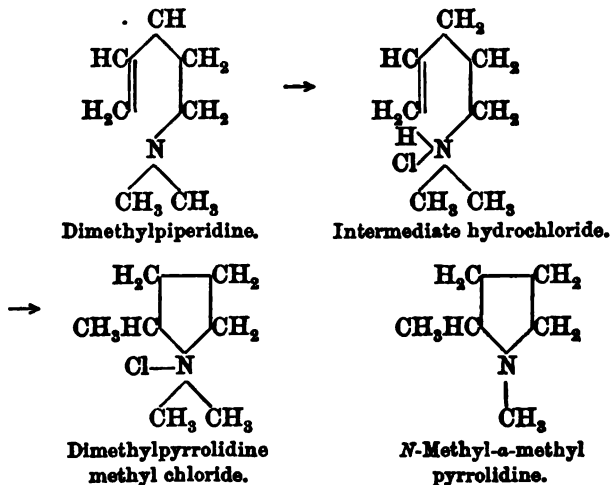


If now the last compound be in turn submitted to a similar series of reactions, the final product decomposes on distillation into piperylene, trimethylamine, and water.



The process is known as 'exhaustive methylation'.

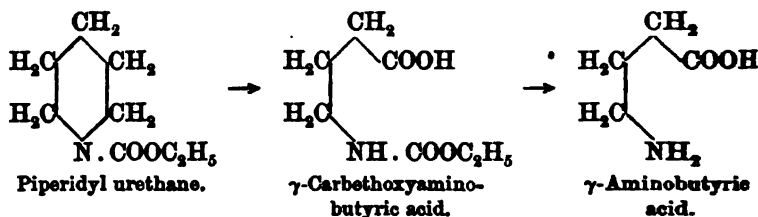
In connection with the open-chain, 'dimethylpiperidine,' Merling¹ has made the interesting observation that on treatment with hydrochloric acid the chain closes, and by isomeric change a dimethyl pyrrolidine methyl chloride is formed, and at a higher temperature methyl chloride is removed and *N*-methyl- α -methyl pyrrolidine results.



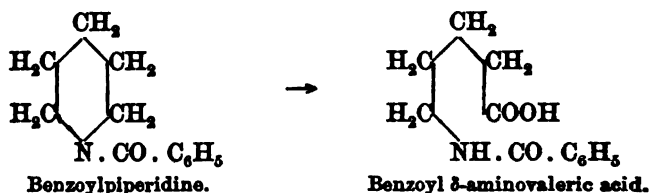
¹ *Annalen*, 1891, 264, 310.

The presence of an acid radical attached to the nitrogen atom in place of hydrogen renders piperidine readily oxidisable, a process by which the ring is ruptured and an open-chain compound produced.

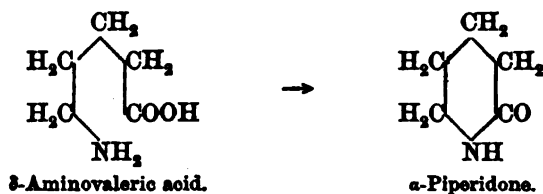
Thus, piperidyl urethane gives on oxidation γ -carbethoxyamino-butyric acid, which splits up with hydrochloric acid into ethyl chloride, carbon dioxide, and γ -aminobutyric acid,



whilst benzoyl piperidine on treatment with potassium permanganate forms benzoyl δ -aminovaleric acid.



The latter process may be reversed, in the sense that, on heating, δ -aminovaleric acid loses water and gives the lactam, α -piperidone.

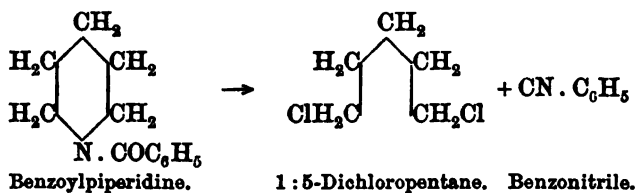


It is an interesting fact that, whereas the open-chain compound is without physiological action, piperidone is a strong poison.

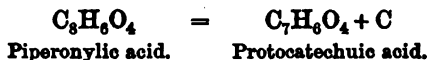
The action of phosphorus pentachloride, which has been recently studied by v. Braun,¹ promises to become a useful addition to the methods of breaking down the cyclic structure in alkaloids.

Benzoylpiperidine with phosphorus pentachloride yields a mixture of benzonitrile and 1 : 5-dichloropentane.

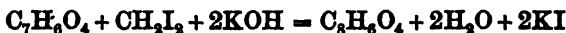
¹ Ber., 1904, 37, 3588.



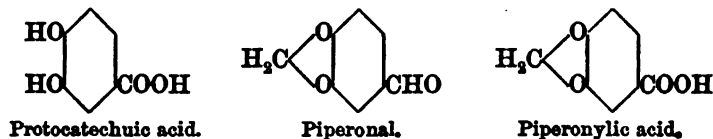
Piperic Acid. The acid constituent of piperine has still to be considered. Our knowledge of its structure is due to Fittig. Piperic acid is a crystalline compound of the formula $\text{C}_{12}\text{H}_{10}\text{O}_4$. It is unsaturated, since it unites with four atoms of bromine, forming a tetrabromo derivative, $\text{C}_{12}\text{H}_{10}\text{Br}_4\text{O}_4$. On reduction with sodium amalgam it forms α - and β -dihydropiperic acid, $\text{C}_{12}\text{H}_{12}\text{O}_4$ (p. 451), and the latter can take up two additional atoms of hydrogen, when the saturated tetrahydropiperic acid is obtained. On oxidation with potassium permanganate it yields two compounds, *piperonal*, $\text{C}_8\text{H}_6\text{O}_3$, and *piperonylic acid*, $\text{C}_8\text{H}_6\text{O}_4$. The former is an aldehyde which readily changes on oxidation into the latter. Piperonylic acid is a saturated acid and decomposes on heating with hydrochloric acid at 170° , or with water at 210° , into protocathechuic acid, carbon being separated.



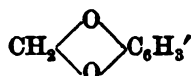
By reversal of the process, Fittig and Remsen succeeded in building up piperonylic acid. This was effected by heating protocathechuic acid with methylene iodide in presence of potash.



The structure of protocathechuic acid being known, the formulæ of piperonal and piperonylic acid probably stand in the following relationship:



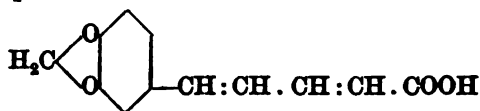
The group 'piperonyl'



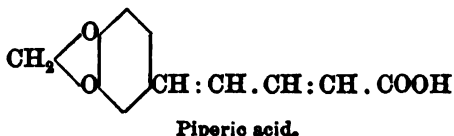
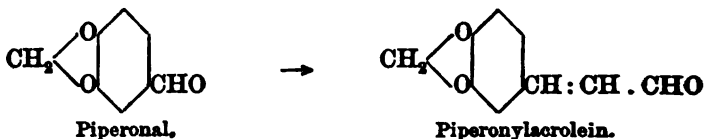
is not an uncommon constituent of vegetable products.

Piperic acid can only possess one side-chain corresponding to the carboxyl group of piperonylic acid, and since its formula is that of

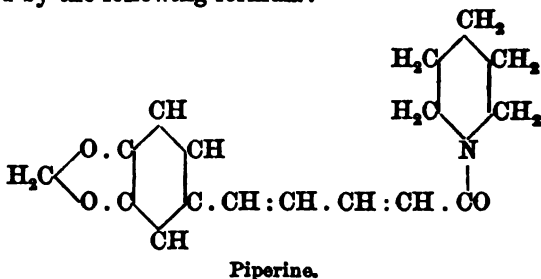
piperonylic acid with the addition of the di-olefinic group C_4H_4 , it is probably represented as follows:



This agrees with the fact that it yields two isomeric dihydro derivatives (p. 178), and also with Doebner's discovery that on careful oxidation it forms piperonal, the side-chain being oxidised to racemic acid. The structure of the acid is further confirmed by its synthesis from piperonal by Ladenburg and Scholtz.¹ Piperonal condenses with acetaldehyde in presence of caustic soda solution. The unsaturated aldehyde, piperonyl acrolein, is then converted by means of Perkin's reaction into piperic acid.



The complete structure of the alkaloid, piperine, is therefore represented by the following formula:



Conine. Hemlock (*conium maculatum*) contains the alkaloid conine, $C_8H_{17}N$, associated with smaller quantities of four other related substances, γ -coniceine, $C_8H_{16}N$, conhydrine, $C_8H_{17}NO$, the isomeric pseudoconhydrine, and *N*-methyl conine, $C_9H_{19}N$. It occurs in the plant in combination with malic and caffeic acids. The largest quantity (about 1 per cent.) is present in the unripe fruit, from which it

¹ Ber., 1894, 27, 2958.

may be obtained, along with the other bases present, by distillation with potash. It is a volatile oil with a penetrating and unpleasant smell, and is extremely poisonous. It is dextro-rotatory, $[\alpha]_D = +18.8^\circ$. Conine was discovered by Giesecke in 1827, but its composition was not accurately known until 1881, when Hofmann began his classical investigation, which ultimately disclosed the true constitution of this interesting alkaloid. In 1885 he pronounced it to be *α -propyl piperidine*. The synthesis of the alkaloid—the first to be obtained artificially, was accomplished by Ladenburg in the year 1886.¹

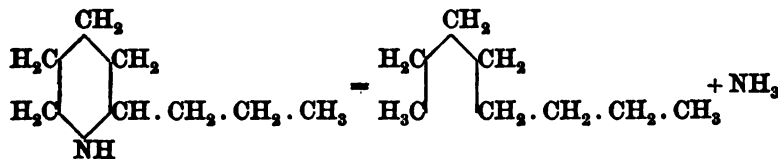
It would occupy too much space to do full justice to Hofmann's researches, which are contained in six papers published during the years 1881–5²; but it should be remembered that the path of inquiry which he pursued was then almost untrodden, and the obstacles which beset the pioneer in such an unknown region could only be surmounted by rare ingenuity and unflinching resource.

The constitution of conine is mainly based upon the behaviour of the hydrochloride with heated zinc dust. Contrary to the usual effect of this reagent, hydrogen is removed and conine forms a new base, *congrine*.



This compound yields picolinic acid on oxidation, and consequently contains a propyl or isopropyl side-chain in the α -position. The choice between propyl and isopropyl pyridine is fixed by a comparison with the artificially prepared compounds and by the products of oxidation and reduction of conine itself.

Strong hydriodic acid converts conine into ammonia and normal octane, which could only occur if the side-chain formed a normal linkage.



n-Propyl piperidine.

n-Octane.

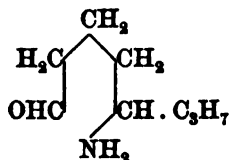
The oxidation products of the urethane and benzoyl derivatives of conine obtained by Schotten and also by Baum³ which correspond to those of piperidine (p. 560) also indicate the presence of a normal

¹ *Ber.*, 1886, 19, 489, 2578. *Annalen*, 1888, 247, 1; 1894, 279, 844.

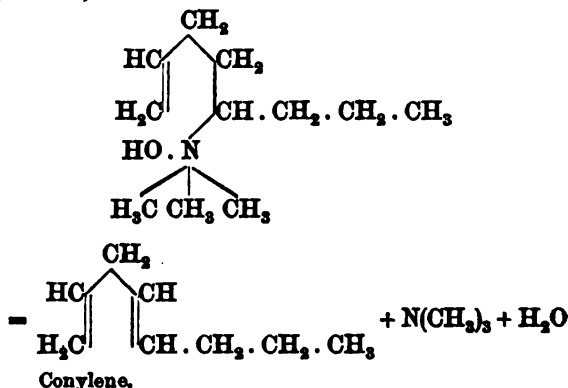
² *Ber.*, 1881, 14, 705; 1882, 15, 2818; 1883, 16, 558; 1884, 17, 825; 1885, 18, 109.

³ *Ber.*, 1882, 15, 1947; 1886, 19, 502.

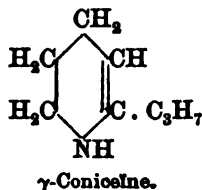
propyl group, whilst by the use of hydrogen peroxide, Wolfenstein¹ obtained among other products amino-*n*-propyl valeric aldehyde.



The evidence adduced by the process of exhaustive methylation points in the same direction, for on distilling the methyl hydroxide of dimethyleconine, which is prepared like the corresponding compound of piperidine, it decomposes into a hydrocarbon *conylene*, trimethylamine, and water.



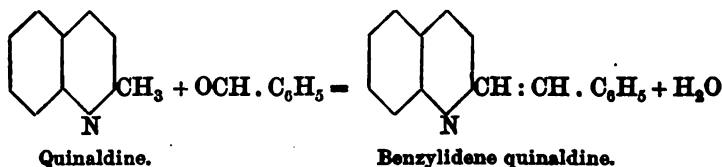
The substances described as *conicefines*, of which Hofmann prepared five isomers, are intermediate reduction products between conyryne and conine, and have the formula $\text{C}_8\text{H}_{15}\text{N}$. γ -Conicefine, which is found in crude conine, can be prepared by the action of alkalis on chloro- or bromo-conine, and, since it is inactive, probably has the formula:



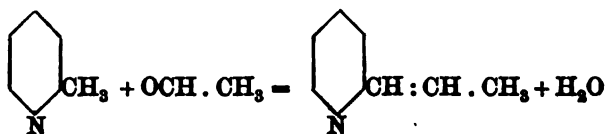
Synthesis of Conine. We have now to follow the steps by which Ladenburg with admirable perseverance succeeded in building up the artificial compound. The attempt to obtain a propyl

¹ Ber., 1895, 28, 1460; 1904, 37, 8223.

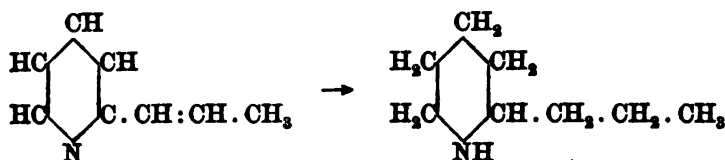
pyridine by heating the propyl iodide compound of pyridine (p. 587) failed, because in the process an intramolecular change occurs, the normal propyl passing into the isopropyl group. The second method met with greater success. It was based upon an observation of Jacobsen and Reimer,¹ who found that when heated together quinaldine condenses with aldehydes and ketones to form alkylidene quinaldines. With benzaldehyde, benzylidene quinaldine is formed :



If α -picoline is substituted for the base and acetaldehyde or paraldehyde for benzaldehyde, and the two heated to 250° , then a small yield of α -allylpyridine is obtained.



Allyl pyridine is reduced in alcoholic solution by sodium and converted into α -propyl piperidine.



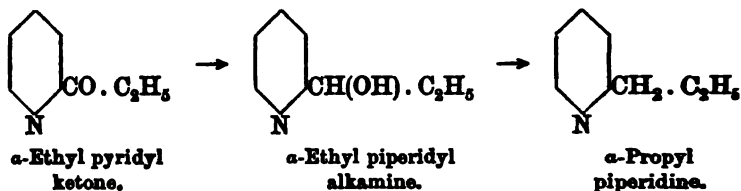
The compound is nearly identical with the natural alkaloid ; in one important property only is it lacking. The natural compound is dextrogyrate, whereas the artificial product is inactive. It is manifest that in propyl piperidine the carbon atom of the nucleus to which the side-chain is attached is asymmetric (p. 68). The artificial compound is probably the racemic form and capable of separation into two active constituents. This was the view taken by Ladenburg, and after many trials he succeeded in separating the dextro- and laevo-components by utilizing the different solubilities of the bitartrates. The dextro-base proved in every respect identical with natural conine.

A few years later Ladenburg's results were confirmed by a second synthesis by Engler and Bauer.² By distilling molecular equivalents

¹ Ber., 1883, 16, 518, 1082, 1892, 2602, 2942.

² Ber., 1891, 24, 2580 ; 1894, 27, 1775.

of the calcium salts of propionic and picolinic acids, they obtained α -ethyl pyridyl ketone, which on reduction is converted successively into α -ethyl piperidyl alkamine and inactive α -propyl piperidine.

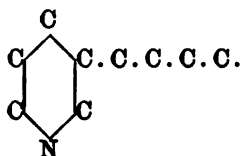


THE PYRROLIDINE ALKALOIDS

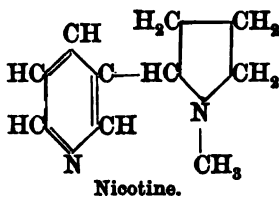
Nicotine is the alkaloid of tobacco leaves, and, like conine, it is associated with small quantities of other, probably similarly constituted, substances. The alkaloid is found in the plant in combination with malic and citric acid, and the quantity varies between 0.6–8 per cent., good leaves containing less than inferior specimens. It is an oil, which boils at 247° , and is a powerful poison, even in the form of vapour. It is laevogyrate. It was originally discovered by Posselt and Reimann in 1828, but its true formula ($\text{C}_{10}\text{H}_{14}\text{N}_2$) was first ascertained by Melsens. Nicotine has been the subject of prolonged and careful study, chiefly by Blau and Pinner, and later by Pictet, who, in 1904, in conjunction with Rotschy, succeeded in preparing it artificially, thereby confirming the structural formula arrived at by Pinner's researches. We propose to follow the principal steps which have led to the knowledge of the structure and ultimately to the synthesis of nicotine, omitting those reactions which have a less important bearing on the problem before us.

Nicotine is a di-acid and also a bi-tertiary base, for it unites with two molecules of alkyl iodide, and likewise forms two different quaternary compounds containing one molecule of methyl iodide. Of the latter, one is obtained by the action of methyl iodide on the hydriodide of the base. When transformed into the quaternary hydroxide and oxidised, Pictet and Genequand obtained trigonelline (p. 541), from which it follows that pyridine is of the two the weaker basic group. The stronger oxidising agents convert nicotine into nicotinic acid, that is, β -pyridine carboxylic acid. Milder oxidising agents like silver oxide or potassium ferricyanide yield *nicotyrins* $\text{C}_{10}\text{H}_{10}\text{N}_2$, whilst hydrogen peroxide gives a substance $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}$ of unknown constitution which is named *oxynicotine*. Thus far, we may conclude that one basic group is pyridine, and that it is

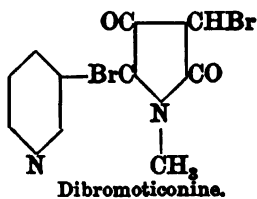
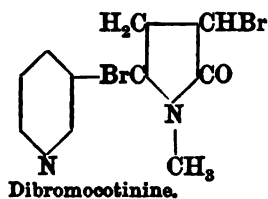
linked in the β -position to the second basic group. The nature of this second group is mainly derived from Pinner's researches on the bromination of nicotine, which will now be considered. At ordinary temperatures nicotine gives a perbromide, $C_{10}H_{11}Br_5N_2O$, from which water or ammonia easily removes three of the bromine atoms (one as hydrogen bromide), forming *dibromocotinine* $C_{10}H_{10}Br_2N_2O$. By the action of bromine at 100° the hydrobromide of *dibromoticonine* $C_{10}H_8Br_2N_2O_2$ is formed. Both compounds are decomposed by bases; the first breaks up into methylamine, oxalic acid, and the base C_7H_7NO , which is probably β -methyl pyridyl ketone, the second forms methylamine, malonic and nicotinic acids. These facts afford valuable information. The second basic group contains one carbon atom as methyl united to a nitrogen atom. The simultaneous appearance of malonic and nicotinic acid among the fragments of bromoticonine imply a β -pyridine side-chain of four carbon atoms, and hence will possess a skeleton structure of the following character :



Seeing that nicotine is a bitertiary base, Pinner concluded that the atoms of the second basic group were fused into a methyl pyrrolidine nucleus thus :

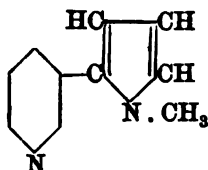


Nicotine therefore represents a β -pyridyl- α -*N*-methylpyrrolidine. Let us examine in the light of this formula the behaviour of nicotine on bromination. According to Pinner, dibromocotinine and dibromoticonine are probably represented by the following formulae :



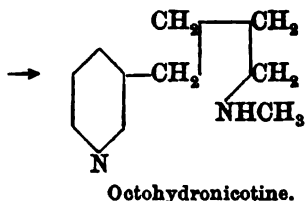
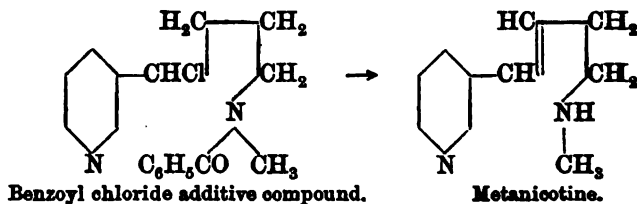
The action of bases on these two substances would be to replace bromine by hydroxyl. This would be followed by a rupture of the pyrrolidine nucleus and the formation of pyridyl methyl ketone and oxalic acid in the first case and of nicotinic and malonic acid in the second.

The other properties of nicotine are also easily explained. Nicotyrine, which contains 4 hydrogen atoms less than nicotine, will probably be represented by the following formula:



Nicotyrine.

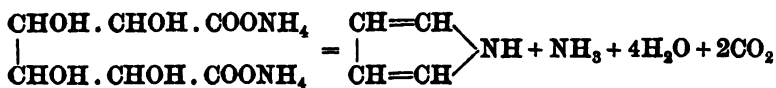
whilst hexahydronicotine, which is obtained by the reduction of nicotine with sodium in alcohol solution, will correspond to the piperidine derivative. The production of the octohydronicotine, which is also formed on reduction, can only be explained by the rupture of the pyrrolidine nucleus. This is confirmed by the following fact. The additive compound of nicotine with benzoyl-chloride is converted by sodium alcoholate into *metanicotine*, a base isomeric with nicotine which on reduction gives octohydronicotine. The explanation is denoted by the following formulae:



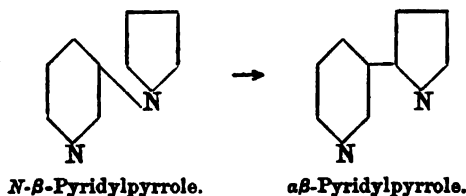
Synthesis of Nicotine. The merit of this achievement belongs to Pictet, Crépieux, and Rotschy.¹ The steps in the discovery are

¹ *Ber.*, 1895, 28, 1904; 1904, 37, 1225.

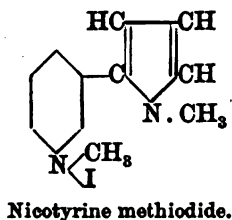
briefly as follows: Pictet and Crépieux obtained *N*- β -pyridyl pyrrole by the distillation of β -aminopyridine mucate, a reaction which corresponds exactly to the formation of pyrrole from ammonium mucate.



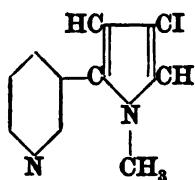
According to an observation of Ciamician the *N*-alkyl derivatives of pyrrole like those of pyridine undergo molecular change on heating by the shifting of the radical from the nitrogen to the α -carbon. By passing the vapour of *N*-pyridylpyrrole through a red-hot tube it isomerises to $\alpha\beta$ -pyridylpyrrole.



By the action of methyl iodide on the potassium salt of the latter $\alpha\beta$ -pyridyl-*N*-methylpyrrole methiodide is formed, which is identical with nicotyrine methiodide.

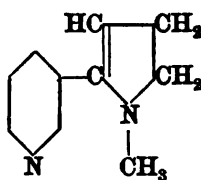


As nicotine contains four atoms of hydrogen more than nicotyrine, which may be regarded as its first oxidation product, the next problem was to reduce nicotyrine. This cannot be effected directly; but by the action of iodine and caustic soda on nicotyrine from natural nicotine a crystalline iodine substitution product is obtained (I), which can be reduced with zinc and hydrochloric acid to dihydronicotyrine (II). The last two hydrogen atoms can be introduced by the reduction of the perbromide of dihydronicotyrine (III).



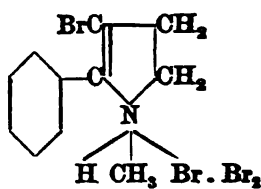
I

Iodide of Nicotyrine.



II

Dihydronicotyrine.



III

Dihydronicotyrine
perbromide.

The new base appeared to be identical with inactive nicotine. The final problem was how to isolate the artificial nicotyrine from its methiodide. After several unsuccessful trials this was eventually accomplished by distilling it with lime at as low a temperature as possible. Inactive nicotine was then prepared from the product in the manner described above and resolved like inactive conine into its active components by crystallizing the tartrates. A comparison of synthetic *l*-nicotine with the natural alkaloid showed complete identity. The difference in the physiological action between the *d*- and *l*-nicotines is remarkable and has been referred to already on p. 77.

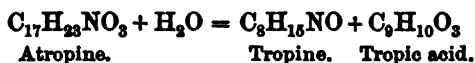
Atropine. Some of the Solanaceae—deadly night-shade or belladonna (*atropa belladonna*), henbane (*hyoscyamus niger*), thorn-apple (*datura stramonium*) and an Australian plant, *duboisia myoporoides*—contain several alkaloids which are closely related in chemical and physiological properties. Four of these, *atropine*, *hyoscyamine*, *pseudohyoscyamine* and *hyoscyne* are isomeric, and have the formula $C_{17}H_{23}NO_3$; the others, *belladonine*, *apoa tropine* $C_{17}H_{21}NO_2$ and *scopolamine* $C_{17}H_{21}NO_4$, are little known. The most important are atropine and hyoscyamine, which are present in all the plants named and in all parts of the plant, though the total quantity is small and rarely exceeds one-half per cent.

Atropine and hyoscyamine, to which we shall confine our attention, are usually extracted from the root of the deadly night-shade with alcohol, from which, after precipitating the colouring matter and removing the alcohol by distillation, the bases are set free with potassium hydroxide and extracted with chloroform.

It may be stated at once that hyoscyamine is the laevo modification of atropine which represents the inactive racemic form, so that in the description of the general chemical properties and structure both compounds are included.

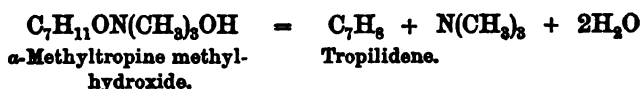
Atropine is a crystalline compound which partly sublimes on heating. It is extremely poisonous and is optically inactive. It

acts as a mydriatic, that is, it causes dilation of the pupil and is universally used in the examination and treatment of diseases of the eye. Atropine was discovered in 1881 almost simultaneously by Mein and by Geiger and Hesse. In 1868 Kraut, and a year later Lossen, succeeded in hydrolysing the substance with alkali or acid into a base, *tropine*, and an acid, *tropic acid*.



Some years later, Ladenburg effected a partial synthesis of the alkaloid by heating tropine tropate, $\text{C}_8\text{H}_{15}\text{NO} \cdot \text{C}_9\text{H}_{10}\text{O}_3$, with dilute hydrochloric acid on the water-bath. A molecule of water is removed and atropine regenerated. The same reaction was repeated with other organic salts and a series of compounds called *tropenes* were prepared, many of them possessing a mydriatic action. One of these compounds, *homatropine*, the tropeine of mandelic acid, has been introduced into ophthalmic practice. It acts as promptly though not as energetically as atropine, but its effects subside more rapidly.

Tropine. We will consider first the properties and structure of the base, tropine, and then direct our attention to those of tropic acid. Our knowledge is chiefly due to the labours of Ladenburg and Merling and to the later researches of Willstätter, and afford a brilliant example of close deduction and skilful experimentation extending over many years. Tropine is a colourless, crystalline and hygroscopic substance. It is a tertiary base which on distillation with soda-lime affords a variety of products, among which methylamine has been identified. The nitrogen atom is therefore linked to a methyl group. At the same time a hydrocarbon, *tropilidene*, C_7H_8 , is formed. The latter has likewise been obtained by the process of 'exhaustive methylation'. The reaction described under piperidine, by which the compound is broken up into trimethylamine and piperylene, can be applied with a similar result to tropine. Tropine methiodide when converted into the methylhydroxide and distilled yields the new base α -methyltropine, $\text{C}_9\text{H}_{17}\text{NO}$. By a repetition of the process the methylhydroxide of this base is obtained, which decomposes on distillation into trimethylamine, tropilidene, and water. The mechanism of this reaction will be referred to later (p. 575).

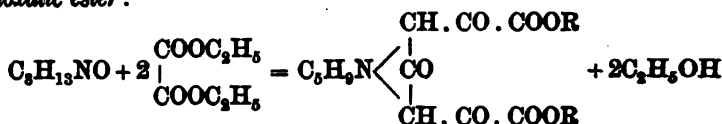


A more interesting compound is *tropidine*, $\text{C}_8\text{H}_{13}\text{N}$, which was

obtained by Ladenburg by heating tropine with hydrochloric acid at 180° , with dilute sulphuric acid at 220° , or with potassium hydroxide, whereby a molecule of water is removed.



It is also formed by the action of hydriodic acid and phosphorus at 140° . It is an unsaturated compound uniting with one molecule of hydrogen, the halides and halide acids. The above facts point to the existence of a *hydroxyl group* in tropine. That the group is present in the form of a *secondary alcohol*, is shown by the oxidation of tropine to the ketone *tropinone* $\text{C}_8\text{H}_{13}\text{NO}$. Reduction of tropinone does not, however, regenerate tropine, but the stereoisomer, ψ -tropine, which is identical with a product obtained from an alkaloid associated with cocaine. Protracted oxidation with chromic acid converts tropinone into the dibasic *tropinic acid*, $\text{C}_8\text{H}_{11}\text{N}(\text{COOH})_2$, which is also obtained by the action of permanganate on tropidine. Furthermore, the ketone group of tropinone is situated between two methylene groups; for the reactions of the complex, $\text{CH}_2 \cdot \text{CO} \cdot \text{CH}_2$, are characteristic, and are consistent with the behaviour of tropinone.¹ For example, tropinone undergoes condensation with two molecules of benzaldehyde, forming a dibenzylidene compound; with two molecules of oxalic ester in presence of sodium ethoxide, giving *tropinone dioxalic ester*:



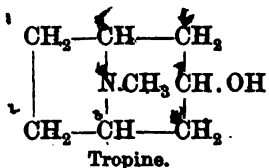
with amyl nitrite in presence of acetic and hydrochloric acid, yielding *diisonitrosotropinone*. Finally, tropinone combines with two molecules of diazobenzene.

The existence of a pyridine, or more accurately piperidine, nucleus in tropine has been demonstrated by Ladenburg² in various ways. He heated tropidine hydrobromide with bromine to 170 – 180° and obtained α -methyl dibromopyridine, and also by using an excess of bromine, Hofmann's dibromopyridine. Further, he found that tropidine on reduction is converted into *hydrotropidine*, $\text{C}_8\text{H}_{16}\text{N}$, which breaks up when heated in a current of hydrogen chloride into *norhydrotropidine* and methyl chloride. When distilled over zinc dust, the latter loses hydrogen and yields α -methyl pyridine. Let us

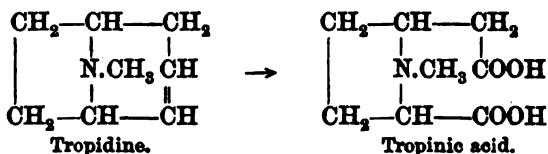
¹ Willstätter, *Ber.*, 1897, 30, 2679.

² *Annalen*, 1883, 217, 144.

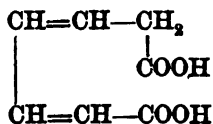
now review the evidences of structure which the above facts afford. The formula for tropine, $C_8H_{15}NO$, includes a tertiary *N*-methyl pyridine nucleus, CH_3NC_5 , and the group, $CH_2 \cdot CH(OH) \cdot CH_2$. Without discussing the views of Ladenburg and Merling, which rested on the incomplete knowledge of earlier researches, we will pass at once to the consideration of Willstätter's formula, which is the result not only of a more extended inquiry into the products of disintegration of tropine, but of the more convincing evidence afforded by its subsequent synthesis:



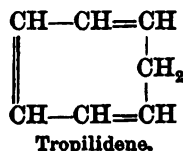
According to this formula, tropine not only contains a hydroxy-*N*-methylpiperidine, but also a pyrrolidine nucleus, as well as a carbon ring of seven atoms. Have we any evidence of the presence of these two nuclei? It seems not improbable that tropinic acid, the product of oxidation of tropidine, is represented by the formula, which is that of a pyrrolidine derivative:



For by Hofmann's method of exhaustive methylation applied to tropinic acid, by which nitrogen is removed as trimethylamine, a diolefinic dibasic acid, $C_5H_6(COOH)_2$, results, which on reduction yields normal pimelic acid, and has undoubtedly the following structure:

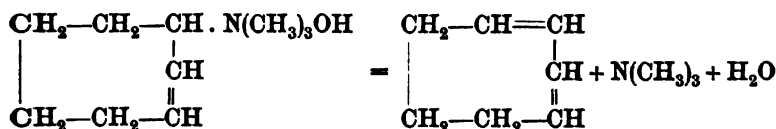


The cycloheptane ring is probably represented by tropilidene, C_7H_8 , which is obtained by the exhaustive methylation of tropine and tropidine (p. 578).

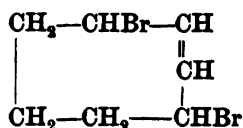


The fact that tropilidene gives benzaldehyde on oxidation, and

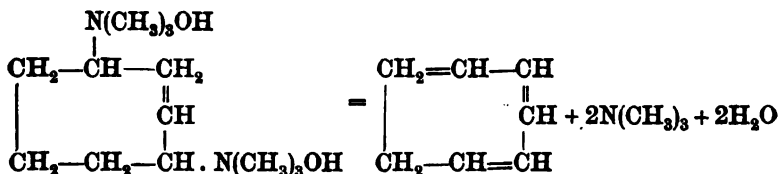
The latter is converted into the quaternary ammonium iodide and hydroxide, and then distilled, when it breaks up into trimethylamine, cycloheptadiene, and water.



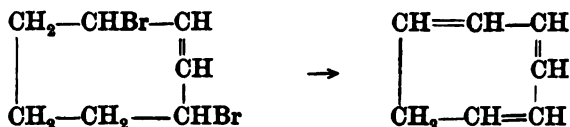
Cycloheptadiene contains a conjugated system of double bonds (p. 452), and with one molecule of bromine forms a dibromide, from which cycloheptatriene can be obtained in two ways.



Dimethylamine combines to form a di-acid base which, by exhaustive methylation, gives cycloheptatriene as follows:

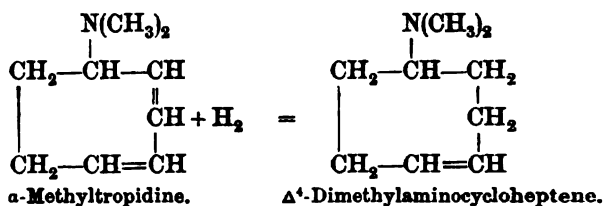


Or hydrogen bromide may be directly eliminated by boiling with quinoline.

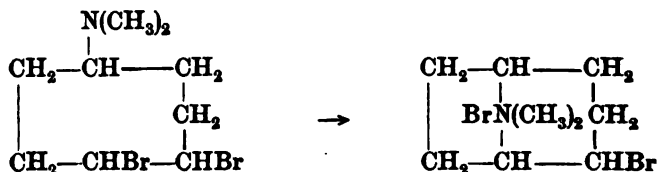


The cycloheptatriene obtained in this way is identical in every respect with Ladenburg's tropilidene (p. 578).

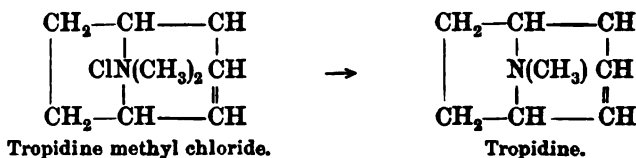
The next step in the synthesis consists in the conversion of tropilidene into tropidine. Cycloheptatriene forms a monohydrobromide with hydrogen bromide in the cold, and the hydrobromide reacts with dimethylamine, giving a product which is identical with α -methyltropidine, obtained by distilling tropidine methyl ammonium hydroxide. This is converted into Δ^4 -dimethylaminocycloheptene on reduction.



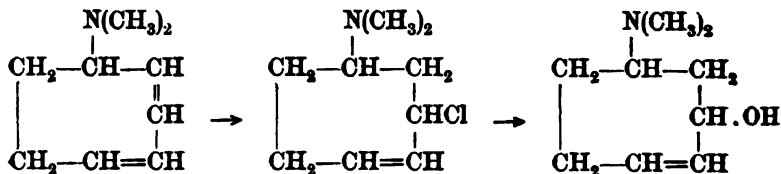
Δ^4 -Dimethylaminocycloheptene unites with a molecule of bromine in the cold, which, on warming, rapidly isomerises to bromotropane-methylammonium bromide.¹



Potassium hydroxide readily removes hydrobromic acid from the latter and converts it into tropidine methylammonium bromide. From the corresponding chloride, methyl chloride may be removed and tropidine itself obtained by distillation.

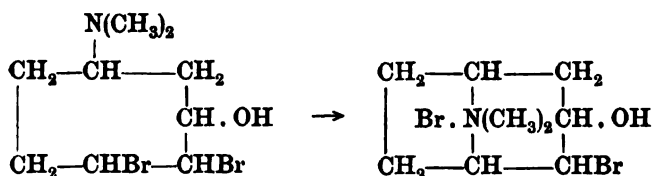


Cycloheptatriene can be converted into tropidine in a different way. Starting from α -methyltropidine described above, the additive compound with hydrogen chloride is treated with sodium bicarbonate solution and the chlorine exchanged for hydroxyl.

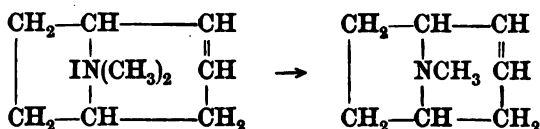


The product is combined with bromine, and when separated from its salt isomerises to bromotropine methyl bromide.

¹ Tropane is the name given to the simple saturated bi-cyclic complex.

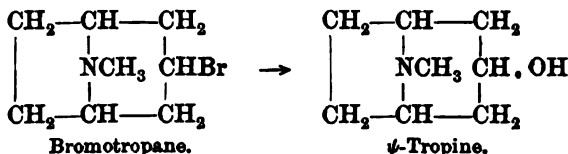


By the action of zinc dust and strong hydriodic acid solution both bromine and hydroxyl are eliminated from the cycloheptane ring and tropidine methyl iodide is formed,



from which tropidine is generated by distillation under diminished pressure.

The conversion of tropidine into ψ -tropine was effected by Willstätter¹ in the following way: Tropidine was combined with hydrogen bromide and heated with sulphuric acid in a closed tube to 200°.



The conversion of ψ -tropine into its stereoisomer tropine was accomplished by oxidising ψ -tropine to tropinone and reducing the ketone with zinc dust and hydriodic acid. Ladenburg² has also transformed tropidine into tropine directly by the action of hydrogen bromide.

Structure and Synthesis of Tropic Acid. It has already been stated that tropic acid is formed with tropine when atropine is hydrolysed. Kraut found that it gave benzoic acid on oxidation, and when fused with potassium hydroxide breaks up into phenylacetic and formic acids. When treated with phosphorus pentachloride, tropic acid exchanges two hydroxyl groups for chlorine,

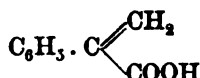


and when heated to 160° it loses a molecule of water and forms the lactone *tropide*, $\text{C}_9\text{H}_8\text{O}_2$, which is converted into the isomeric *atropic*

¹ Ber., 1900, 33, 1170.

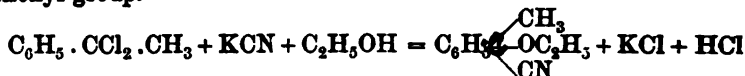
² Ber., 1890, 23, 1780, 2225; 1902, 35, 1159, 2295.

acid on boiling with baryta water. That atropic acid is a benzene derivative with one side-chain follows from the fact that it yields benzoic acid on oxidation. Moreover, it is unsaturated, forming additive compounds with one molecule of hydrogen bromide or bromine. It is therefore closely related to cinnamic acid, with which it is in fact isomeric, and is probably represented by the formula,

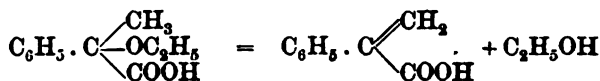


This structure has been confirmed by its synthesis by Ladenburg and Rügheimer¹ in 1880.

Acetophenone is converted into the dichloride by the action of phosphorus pentachloride. When the dichloride is treated with an alcoholic solution of potassium cyanide, a double reaction occurs, one chlorine atom being replaced by cyanogen and the other by the ethoxyl group.



The product being a cyanide can be hydrolysed, and the resulting ethyl α -phenyllactic acid, when heated with strong hydrochloric acid, loses a molecule of alcohol and yields atropic acid.



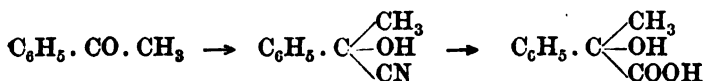
Atropic acid is clearly the anhydride of tropic acid. By the addition of the elements of water the hydroxyl may attach itself to the end or middle carbon atom of the side-chain. Two isomers must therefore exist of the following formulae:



An acid having the first of these formulae has long been known under the name of *atrolactic acid*. It was obtained originally by Fittig and Wurster by heating with sodium carbonate the hydrogen bromide additive compound of atropic acid. Later it was synthesized and its structure ascertained by Spiegel² by the simple process of hydrolysing the cyanhydrin of acetophenone.

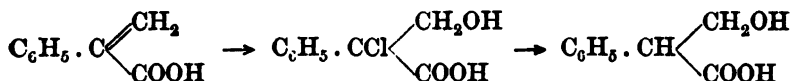
¹ Ber., 1880, 13, 373, 2041.

² Ber., 1881, 14, 1853.



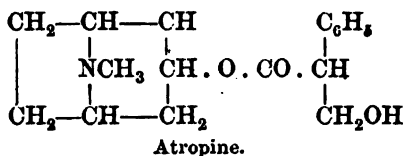
Consequently the second of the two formulae must be that of tropic acid. This view has been fully confirmed by its synthesis from atropic acid.

Atropic acid unites with hypochlorous acid, and the additive compound on reduction forms tropic acid.



According to this formula, tropic acid contains an asymmetric carbon, and it has been resolved into its two enantiomorphs by crystallizing the quinine salt.

Structure of Atropine. The fact that the hydrolysis of atropine produces tropine which possesses alcoholic functions and an acid, tropic acid, shows that the alkaloid itself must be an ester. This structure finds expression in the following formula:



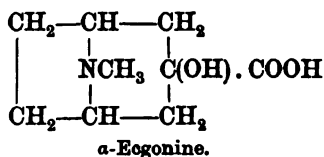
Hyoscyamine, according to the researches of Gadamer,¹ is the ester of tropine and *l*-tropic acid; Hesse and Ladenburg have shown that *atropamine* is the tropeine of atropic acid, which undergoes isomerisation into *belladonine* on heating, whilst, according to Liebermann, the coca alkaloid, *tropacocaine*² (see below), is the benzoic ester of ψ -tropine. All these substances must now be included in the list of synthetic products.

Cocaine. The leaves of *erythroxylon coca* contain a series of alkaloids, among which *l*-cocaine, *d*-cocaine, *tropa-cocaine*, *cinnamyl-cocaine*, *truxilline* and *hygrine* have been identified as distinct constituents. *l*-Cocaine, the most abundant and physiologically the most valuable constituent (it acts as a local anaesthetic), was isolated by Niemann as far back as 1860, and its formula, $\text{C}_{17}\text{H}_{21}\text{NO}_4$, was ascertained by Lossen. In recent years the study of the alkaloid has been pursued

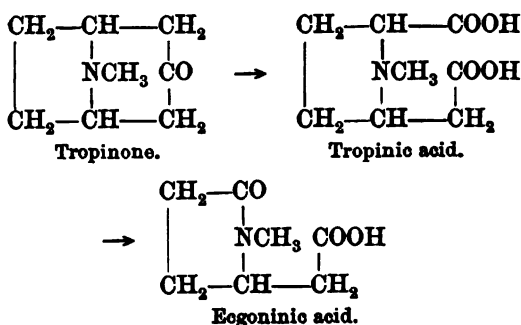
¹ *Arch. d. Pharm.*, 1902, 239, 294.

² Liebermann, *Ber.*, 1891, 24, 2336.

isotropylamine. It follows, therefore, that the carboxyl group does not occupy the position of the hydroxyl in tropine. Furthermore, the hydroxyl group in ecgonine is not attached to the same carbon atom as the carboxyl, for tropinone cyanhydrin gives on hydrolysis a compound similar to, but distinct from, ecgonine, which is therefore named α -ecgonine, giving an α -methyl benzoyl ester known as α -cocaine.



This is also confirmed by the fact that ecgonine on oxidation with chromic acid gives a ketonic acid, which could only occur if the carboxyl and hydroxyl were attached to different carbon atoms. But there still remains a choice between the β - and γ -positions for the hydroxyl group. There are several facts which favour the β -position, and these are furnished by the products of oxidation. Ecgonine, by careful oxidation with chromic acid, loses carbon dioxide and is converted into tropinone. More energetic oxidation produces tropinic acid (p. 575) and ecgoninic acid. The tropinic acid only differs from the acid from tropine by being optically active (dextrogyrate), whilst the structure of ecgoninic acid is known from its synthesis by Willstätter and Hollander.¹

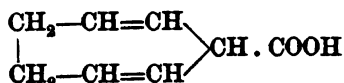


It is clear that the hydroxyl stands in the β -position to the carboxyl group; but if any further doubt existed on the subject, it has been set at rest by the synthesis of *r*-cocaine from tropinone by Willstätter².

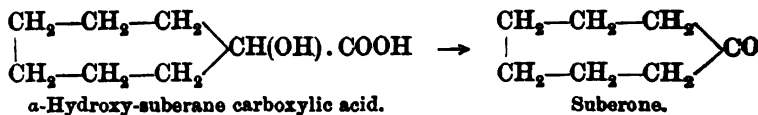
¹ *Annalen*, 1908, 326, 79.

² *Ber.*, 1900, 33, 411; *Annalen*, 1908, 326, 42.

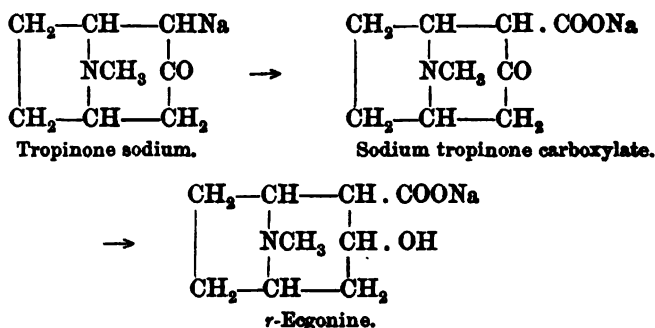
Before referring to the synthesis, it may be of interest to point out that just as tropine furnishes a cycloheptane ring in the form of tropilidene (p. 578), so ecgonidine or, more strictly, hydroecgonidine may be resolved into a cycloheptadiene carboxylic acid by exhaustive methylation and ultimately into suberone. The ethyl ester of hydroecgonidine is first converted into the nitrogen free acid, cycloheptadiene carboxylic ester.



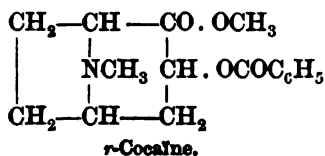
The latter is reduced to the saturated cycloheptane carboxylic acid. Bromine is then introduced in the α -position and replaced by hydroxyl. The hydroxy-acid, when submitted to oxidation with lead peroxide, yields suberone.



Synthesis of *r*-Cocaine. Tropinone sodium, when suspended in ether and treated with carbon dioxide, forms sodium tropinone-carboxylate, and the latter, on reduction with sodium amalgam in faintly acid solution, is converted into *r*-ecgonine and a second isomer.

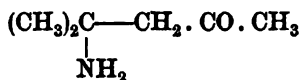


The *r*-ecgonine differs in optical properties from the ecgonine of the vegetable alkaloid; for naturally it is inactive, and, as it contains four asymmetric carbon atoms, may represent several pairs of enantiomorphs. Apart from this, it closely resembles *l*-ecgonine, and, like it, may be converted into the methyl benzoyl ester or *r*-cocaine.

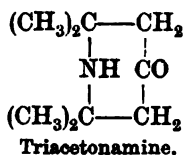


The second isomeric ecgonine which forms the greater portion of the reduction product is probably a ψ -tropine *O*-carboxylic acid; for it contains no hydroxyl group and resists the ordinary process of methylation.¹

Euphthalmine and Eucaine. A very interesting development in synthetic chemistry has arisen out of the knowledge of the structure of atropine and cocaine. The di- and tri-acetonamines are compounds which are obtained by the action of ammonia on acetone, and are represented by the following formulae:

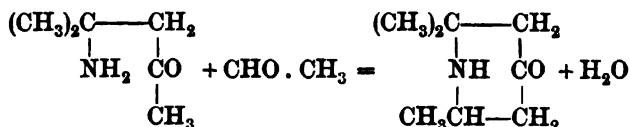


Diacetonamine.



Triacetonamine.

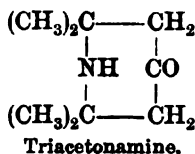
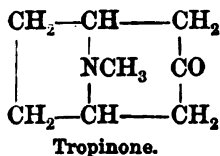
Diacetonamine may be converted into triacetonamine by heating it with acetone. Aldehydes unite in a similar fashion, acetaldehyde forming vinylldiacetonamine.



Diacetonamine.

Vinylldiacetonamine.

The ring complexes formed in this way have a similar structure to tropinone.

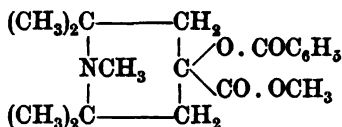


This similarity is not limited to structure, for Harries² has shown that the triacetonamines undergo reduction and form what are known

¹ Willstätter and Bode, *Annalen*, 1908, 326, 45.

² *Annalen*, 1897, 290, 328; V. Coblentz, *J. Soc. Chem. Ind.*, 1898, 725; 1904, 93.

as *triacetonalkamines* corresponding in structure to tropine, and which like tropine, form tropeines with acids. Thus the phenylglycolyl ester of *N*-methyl vinylldiacetonalkamine is used as a substitute for atropine under the name of *euphthalmine*, and has a strong mydriatic action. Similarly, Merling has combined the triacetoneamines with hydrogen cyanide, and by hydrolysing the product obtained hydroxy-acids constituted like ecgonine. These substances, when converted into the benzoyl methyl esters, produce local anaesthesia like cocaine, and are known as *eucaïnes*. A variety of these products has been prepared.



Eucaïne A.

Eucaïne A is derived from triacetoneamine, eucaïne B is the benzoyl ester of vinylldiacetonalkamine.

THE ISOQUINOLINE ALKALOIDS

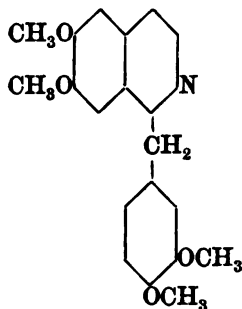
The alkaloids of this group comprise the three opium alkaloids,¹ *papaverine*, *narcotine*, *narceïne*, and the two alkaloids, *hydrastine* and *berberine*, which occur in the roots of golden seal (*hydrastis canadensis*). Berberine, it should be added, is one of the few alkaloids which is distributed among many different orders of plants, such as the common barberry (*berberis vulgaris*), from which it receives its name.

Papaverine. The alkaloid was discovered in 1848 by Merck in commercial narcotine, from which it was separated by crystallizing the hydrochloride, the former being less soluble. Merck gave it the formula $\text{C}_{20}\text{H}_{21}\text{NO}_4$, which other observers have since confirmed.

¹ The following table, which is taken from Pietet's treatise on the *Vegetable Alkaloids*, gives some idea of the complex nature of opium. The list does not exhaust the number of constituents, which embraces more than twenty different individuals, nor does it include the various other ingredients of the dried sap of the poppy such as fats, resins, gums, sugar, and protein matter.

	Per cent.		Per cent.
Morphine	9.0	Laudanine	0.01
Narcotine	5.0	Lanthopine	0.006
Papaverine	0.8	Protopine	0.008
Thebaine	0.4	Codamine	0.002
Codeine	0.3	Iritopine	0.0015
Narceïne	0.2	Laudanosine	0.0008
Cryptopine	0.08	Meconine	0.3
Pseudomorphine	0.02	Meconic acid	4.0
		Lactic acid	1.2

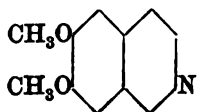
The constitution of papaverine has been studied and completely elucidated by G. Goldschmiedt¹ in a series of brilliant researches which appeared in the *Monatsheft* during the years 1888 to 1888. From the results of his investigations, of which a short abstract is given below, he assigned the following formula to the alkaloid:



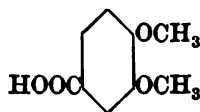
Papaverine.

Papaverine is a tertiary base and optically inactive. It forms no acetyl derivative, and therefore contains no hydroxyl groups. With concentrated hydriodic acid four molecules of methyl iodide are eliminated, and *papaveroline*, $C_{16}H_{13}NO_4$, is produced.

On oxidation with permanganate under varying conditions a variety of products are formed, among which may be mentioned *papaveraldine*, $C_{20}H_{19}NO_6$, *papaveric acid*, $C_{16}H_{13}NO_7$, and simpler compounds derived from these by further oxidation, namely dimethylprotocatechuic acid, metahemipinic acid, dimethoxyisoquinoline carboxylic acid, α -carbocinchomeronic acid, &c. On fusion with alkali, papaveraldine is decomposed into *dimethoxyisoquinoline* and *dimethylprotocatechuic acid*:



Dimethoxyisoquinoline.

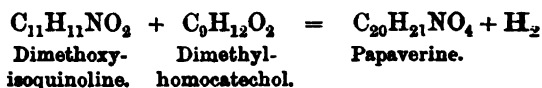


Dimethylprotocatechuic acid.

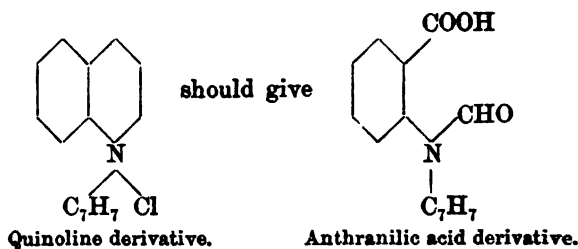
whilst papaverine on fusion with potash yields dimethylhomocatechol and basic substances.

These reactions furnish the key to the structure of the alkaloid. By combining the formula of dimethoxyisoquinoline with that of dimethylhomocatechol, the formula of papaverine is obtained, plus two atoms of hydrogen.

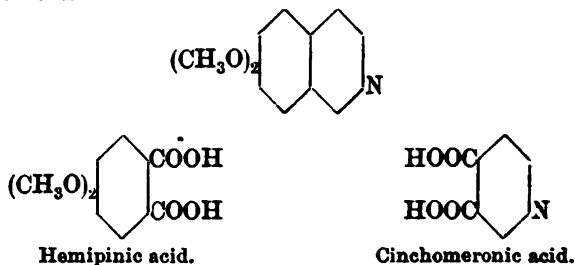
¹ See various papers in *Monatsh.*, 4, 6, 7, 8, 9, 10, 13, 17.



Goldschmiedt at first regarded the isoquinoline compound as a derivative of quinoline until he discovered his error in attempting to ascertain the positions of the two methoxyl groups in dimethoxy-isoquinoline by the oxidation of the additive compound with benzyl-chloride. Instead of the expected derivative of anthranilic acid, he obtained an imide of dimethoxy-phthalic acid (metahemipinic acid).

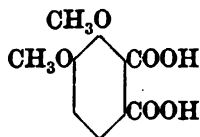


He confirmed this result by oxidising dimethoxy-isoquinoline. If the latter is a quinoline derivative it should yield quinolinic acid; if, on the other hand, it is an isoquinoline compound it should form cinchomeronic acid. It was the second reaction which occurred, the compound breaking up in two directions and forming hemipinic and cinchomeronic acid.



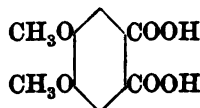
The hemipinic acid formed in this way is so similar to one obtained by Wöhler by the oxidation of narcotine that their identity was at first assumed; but closer examination revealed a slight difference in

properties. Both hemipinic acids readily form anhydrides, and therefore contain the carboxyl groups in the ortho position. Ordinary hemipinic acid, which has been the object of a careful study by Wegscheider, has the formula,



Hemipinic acid.

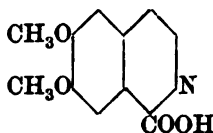
Since the hemipinic acid, which Goldschmiedt calls metahemipinic acid, gives protocatechuic acid on fusion with caustic potash, the only possible structure is:



Metahemipinic acid.

To construct a satisfactory formula for the alkaloid, it is necessary to explain the character of papaverine and the properties of its numerous decomposition products.

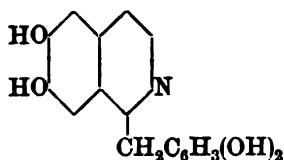
Among the simpler products of oxidation we have still to account for dimethoxy-isoquinoline carboxylic acid and α -cinchomeronic acid. These are clearly related, since they both are derived from an isoquinoline complex. As the formula for α -carbocinchomeronic acid is known, that of dimethoxy-isoquinoline carboxylic acid follows;



Dimethoxy-isoquinoline carboxylic acid.

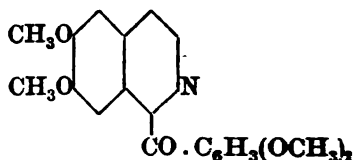
for this is the only position which can be assigned to the carboxyl group consistent with the existence of an isoquinoline group, the formation of metahemipinic acid, and the formula of carbocinchomeronic acid.

The formula for papaverine, already referred to, supplies all the necessary demands on the part of the compounds derived from it. Papaveroline, which is produced by eliminating the methoxyl groups, will have the formula I. Papaveraldine, the first product of oxidation, forms a hydrazone, and exhibits the general behaviour of a ketone, and consequently has formula II.



I

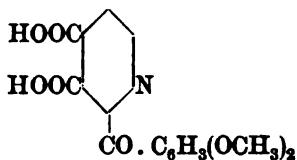
Papaveroline.



II

Papaveraldine.

Papaveric acid is a ketonic dibasic acid, which, on fusion with caustic potash, forms protocatechuic acid, and therefore has the formula :



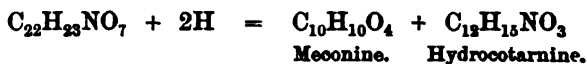
Papaveric acid.

The work of Goldschmiedt on papaverine has prepared the way for the investigation of the other isoquinoline alkaloids which have been attacked by similar methods and with equally successful results.

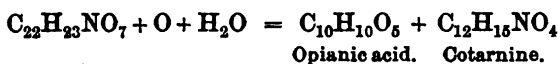
Narcotine was isolated from opium in 1817 by Robiquet. The quantity, which varies considerably (0·75–9 per cent.), may be extracted by simply shaking with ether. The molecular formula assigned by Matthiessen and Foster is $C_{22}H_{23}NO_7$. It is a tertiary base and contains no hydroxyl group, as it reacts neither with acetyl chloride nor acetic anhydride. It contains three methoxyl radicals which may be successively removed. As caustic potash decomposes narcotine at 220° , liberating methylamine, dimethylamine, and trimethylamine, it may be assumed that the nitrogen in the compound is methylated. Narcotine undergoes simple decomposition in three directions. It is hydrolysed by water at 140° , dilute sulphuric, or baryta, and yields *opianic acid* and *hydrocotarnine*.



Reducing agents like zinc and hydrochloric acid break it up into *meconine* and *hydrocotarnine*,

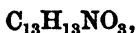


whilst oxidising agents affect the basic part of the molecule and produce opianic acid and *cotarnine*.



We will begin by studying the basic constituent of the molecule.

Structure of Hydrocotarnine and Cotarnine. Cotarnine was first obtained by Wöhler in 1844 by oxidising narcotine with manganese dioxide and sulphuric acid, and he gave it the formula

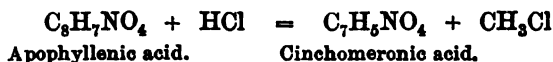


which Matthiessen and Foster afterwards replaced by

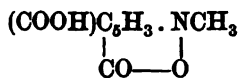


Roser has since shown that the salts of cotarnine contain the basic group, $\text{C}_{12}\text{H}_{13}\text{NO}_3$, united with the acid, and that the molecule of water is constitutional. Cotarnine is a secondary base, and forms an oxime with hydroxylamine hydrochloride. When reduced with zinc and hydrochloric acid it is converted into hydrocotarnine.

One of the most interesting derivatives of cotarnine is *apophyllenic acid*, which is obtained by oxidation, and was so called by Wöhler from the resemblance of the crystals to the mineral apophyllite. It is a monobasic acid of the formula $\text{C}_8\text{H}_7\text{NO}_4 + \text{H}_2\text{O}$. According to Vongerichten, when heated with hydrochloric acid to 250° , it loses methyl chloride and forms cinchomeronic acid.

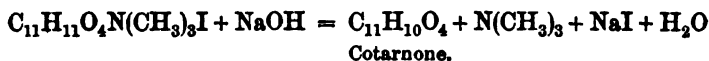


Roser accomplished the reverse synthetic process by boiling cinchomeronic acid with methyl iodide, from which he concluded that apophyllenic acid is the methylbetaine of cinchomeronic acid, leaving undecided which of the two carboxyls takes part in the anhydride formation.



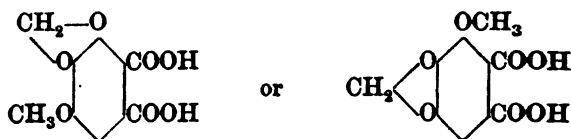
Apophyllenic acid.

The explanation of the structure of cotarnine is mainly due to the researches of Roser.¹ By exhaustive methylation, a methyl iodide of methylcotarnine is obtained, indicating thereby the secondary nature of the base. The hydroxide breaks up on distillation, yielding up its nitrogen as trimethylamine and forming *cotarnone*, a nitrogen-free compound with aldehyde properties.



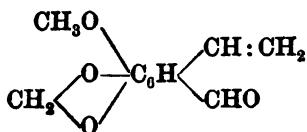
¹ *Annalen*, 1888, 249, 156; 1889, 254, 834.

On oxidation with permanganate cotarnone is converted into the basic *cotarnic acid*, $C_8H_6O_2(COOH)_2$, which Roser, for the reasons given below, regards as having one of the following alternative formulæ:

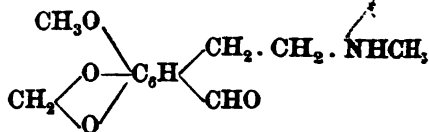


Cotarnic acid.

It forms an anhydride, loses one methyl group by Zeisel's method, and, on being heated with hydriodic acid and phosphorus, is converted into gallic acid. Putting these facts together, the above relationships will be best interpreted by the following formulæ:

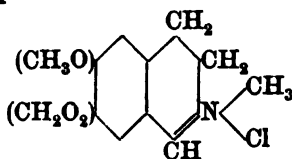


Cotarnone.



Cotarnine.

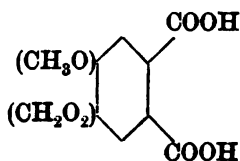
Although cotarnine itself appears not to possess a pyridine nucleus, it is supposed that in its salts ring-formation occurs, and that the hydrochloride of cotarnine is represented by a formula, which is that of a derivative of isoquinoline:



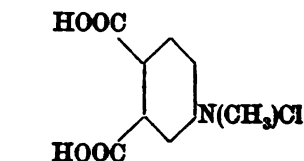
Cotarnine hydrochloride.

According to Dobbie, Lauder, and Tinkler, who have studied the absorption spectrum of cotarnine, the free base exhibits tautomerism (p. 202).

The parallelism between the behaviour of isoquinoline and cotarnine on oxidation is very clearly exhibited by the products of oxidation, for whilst the former gives phthalic and cinchomeronic acids, the latter breaks up into cotarnic and apophyllenic acids.



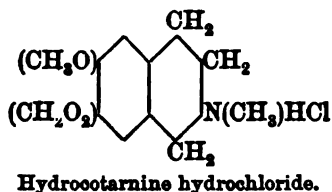
Cotarnic acid.



Apophyllenic acid (hydrochloride).

STRUCTURE OF HYDROCOTARNINE AND COTARNINE 593

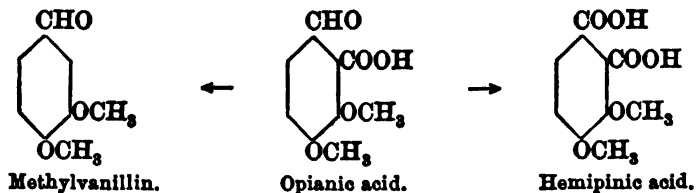
Hydrocotarnine is a reduction product of cotarnine and a tertiary base, and these facts are combined in the following formula:



Opianic Acid. Opianic acid is a monobasic acid having the properties of an aldehyde and containing two methoxyl groups. Its formula may therefore be represented by

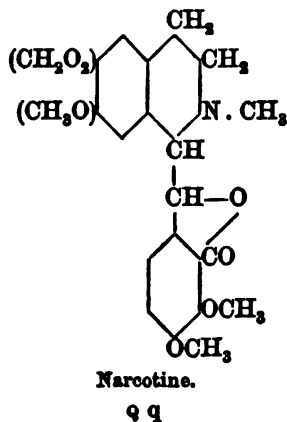


The relative positions of these groups has been ascertained as follows: on distillation with soda-lime it yields methylvanillin, and on oxidation it is converted into hemipinic acid (p. 589).



Finally, *meconine* is the lactone of the alcohol produced by the reduction of the aldehyde group in opianic acid.

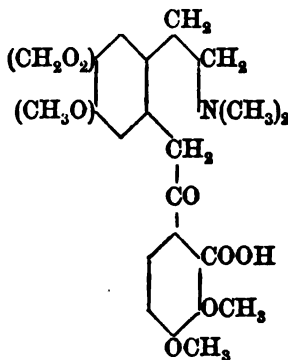
These facts enable us to piece together the various fragments so as to construct a probable formula for narcotine, which has been represented as follows:



Narceïne. The relationship of narcotine to narceïne has been established by Roser's synthesis of the latter from narcotine. When the methyl iodide of narcotine is heated with caustic alkali it yields narceïne.



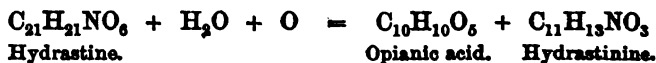
Its other properties are in harmony with the following structural formula:



Narceïne.

We shall close our account of the isoquinoline alkaloids with a short reference to hydrastine and berberine.

Hydrastine. The root of the golden seal (*Hydrastis canadensis*), a plant belonging to the Ranunculaceae and indigenous to N. America, contains about 1.5 per cent. of hydrastine and 4 per cent. of berberine. Hydrastine was first observed by Durand in 1851, and has since been studied by numerous investigators. Our knowledge of its structure is mainly due to the work of E. Schmidt¹ and M. Freund² during the last two decades. It is closely related to narcotine. Like narcotine, it breaks up by acid oxidation into *opianic acid* and *hydrastinine*.



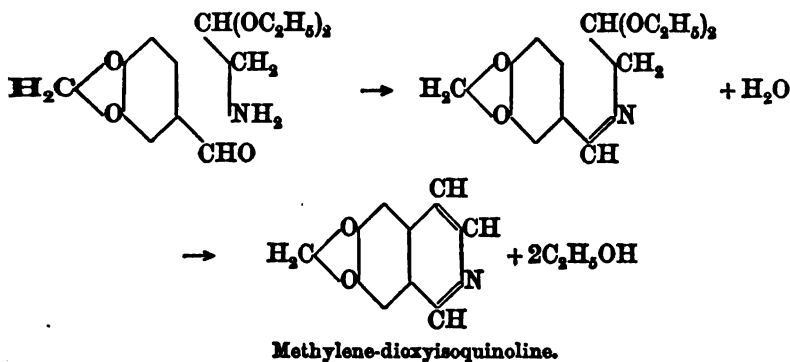
It contains two methoxyl groups, but neither aldehyde nor ketone group nor ethylene linkage.

Hydrastinine only differs from cotarnine by the group CH_2O , which suggests one methoxyl group less in hydrastinine, and leads to

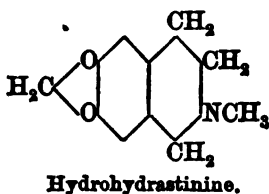
¹ *Archiv d. Pharm.*, 1884, 224, 974; 226, 289; 1885, 228, 49, 221, 596; 231, 541; 1886, 232, 186.

² A summary is contained in *Annalen*, 1892, 271, 811.

the general conclusion that narcotine itself is a methoxy-hydrastine. This view has been confirmed. Hydrastinine on reduction with zinc and hydrochloric acid, sodium amalgam, or by electrolysis, is converted into *hydrohydrastinine*, $C_{11}H_{13}NO_3$, a compound which has been synthesized by Fritsch¹ as follows: piperonal is condensed with amino-acetal, and the product is then treated with sulphuric acid, by which alcohol is removed.

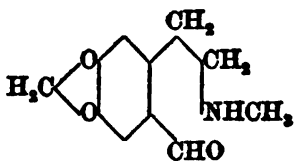


When the methiodide of the last compound is reduced with tin and hydrochloric acid, it is converted into hydrohydrastinine. According to Freund, hydrohydrastinine yields hydrastinine on oxidation with potassium dichromate and sulphuric acid.

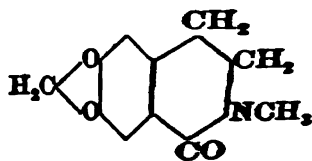


The relation of hydrohydrastinine to hydrastinine follows from the general properties of the latter. It contains an aldehyde group like cotarnine, and, like cotarnine, forms salts with the elimination of a molecule of water. On oxidation it is converted successively into oxyhydrastinine $C_{11}H_{11}NO_3$, hydrastinic acid $C_{11}H_9NO_3$, and finally apophyllenic acid. There are a variety of other products known, but sufficient has been stated to afford a basis for a satisfactory structural formula. The relation of hydrastinine to oxyhydrastinine is represented as follows :

¹ *Annalen*, 1895, 286, 1.

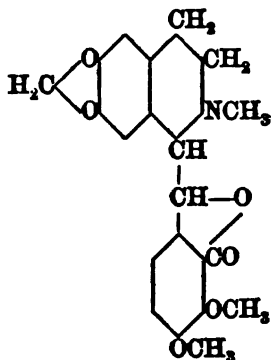


Hydrastinine.



Oxyhydrastinine.

whilst hydrastine has the formula :



Hydrastine.

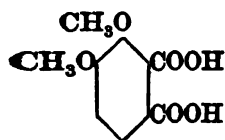
Berberine was discovered in 1826 in prickly ash (*Xanthoxylum clava-herculis*) by Chevalier and Pelletan, who named it *xanthopicrotin*. When Büchner in 1835 found it in barberry root the name was changed to berberine. Since then it has been observed in many other plants, the largest amount (8-9 per cent.) being found in *coptis*. The composition of berberine, $C_{20}H_{17}NO_4$, as well as its constitution, have been worked out very completely by W. H. Perkin, jun.¹ The following are the principal facts upon which its structure rests. Berberine is a tertiary base, and forms salts which have a yellow colour. It contains neither aldehyde, ketone, nor hydroxyl group. Of the two methyl groups, which are removed by Zeisel's method, neither is attached to nitrogen, and they are consequently present as methoxyl.

The most important insight into the structure of berberine is afforded by its products of oxidation. By the action of permanganate in alkaline solution, Schmidt² obtained *hemipinic* and *hydrastic acids*, both of which had been previously prepared from hydrastine; whilst Weidel³ by using concentrated nitric acid obtained *berberonic acid*, or β - γ - α' -pyridine tricarboxylic acid.

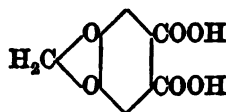
¹ *Trans. Chem. Soc.*, 1889, 55, 63; 1890, 57, 992.

² *Arch. d. Pharm.*, 228, 596.

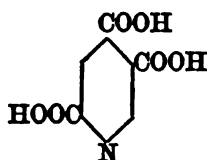
³ *Ber.*, 1879, 12, 410.



Hemipinic acid.



Hydrastic acid.

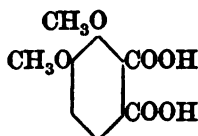


Berberonic acid.

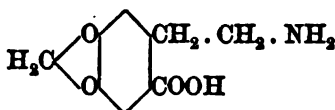
A renewed study of the action of permanganate on berberine by Perkin, jun., led to the isolation of the following series of oxidation products:

Oxyberberine	$C_{20}H_{17}NO_5$	Anhydroberberilic acid	$C_{20}H_{17}NO_3$
Dioxyberberine	$C_{20}H_{17}NO_6$	Berberilic acid	$C_{20}H_{16}NO_3$
Berberal	$C_{20}H_{17}NO_7$	Berilic acid	$C_{20}H_{16}NO_3$

from which oxyhydrastinine was ultimately prepared and a common bond established with narcotine and hydrastine. The most interesting of the above series are *berberilic acid* and *berberal*. Berberilic acid, which is a dibasic acid, breaks up on boiling with dilute sulphuric acid into hemipinic acid and amino-ethyl piperonylic acid.

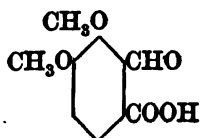


Hemipinic acid.

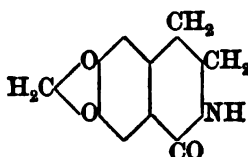


Amino-ethyl piperonylic acid.

In the same way berberal, when treated with alcoholic potash, is resolved into amino-ethyl piperonylic anhydride, $C_{10}H_9NO_3$, and pseudo-opianic acid, $C_{10}H_{10}O_5$. The former is regarded by Perkin as noroxyhydrastinine since it can be converted into oxyhydrastinine.

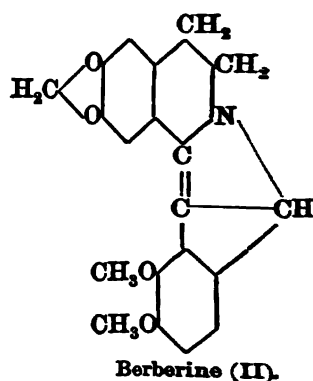
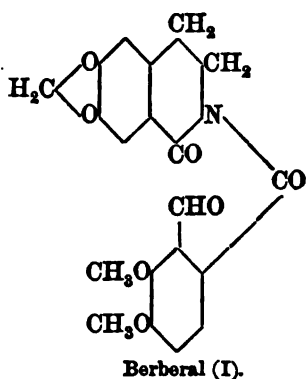


Pseudo-opianic acid.

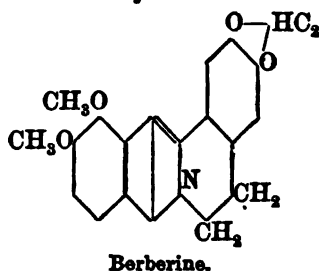


Noroxyhydrastinine.

As berberal is an aldehyde, the union between noroxyhydrastinine and pseudo-opianic acid must be effected through the carboxyl and not through the aldehyde group, and will probably have the following structure I, and berberine will appear as II:



or arranged somewhat differently :



This arrangement contains the group,



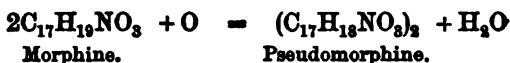
which Perkin regards as the chromophoric group, imparting to berberine salts their yellow colour.

THE MORPHINE ALKALOIDS

This group includes at least four important alkaloids found in opium, namely, *morphine*, *codeine*, *pseudomorphine* and *thebaine*. They are distinguished from the more numerous class of opium alkaloids to which papaverine and narcotine belong, by their poisonous character. In spite of the enormous mass of material which has resulted from the study of these alkaloids, we are still ignorant of their structure. The following pages contain a very general and incomplete summary of the results.

Morphine and Codeine. The structural relationships between morphine and codeine may at once be made clear. The formula for morphine, $C_{17}H_{19}NO_3$, and codeine, $C_{18}H_{21}NO_3$, indicates a difference of a methyl group, and the conversion of the one into the other by Grimaux in 1881 by the action of methyl iodide and caustic potash, and later by that of diazomethane on morphine, leaves no doubt about the correctness of this view.

Morphine, as already stated (p. 584), was the first alkaloid to be isolated. Although the average amount in opium is given in the table (p. 586) as 9 per cent., it varies considerably, and may rise to 20 per cent. or more in some specimens, or fall to 8 per cent. in others. Morphine is a tertiary base and at the same time a monohydric phenol, for it dissolves in caustic alkalis and forms salts with one atom of metal, from which it is again precipitated by carbon dioxide. On the other hand, it forms diacyl derivatives, and therefore contains two hydroxyls, one of which is probably alcoholic in character. The third oxygen is indifferent and is probably present as an anhydride or ether group. Morphine is very oxidisable, reducing certain metallic salts and separating iodine from iodic acid. The product of these and other weak oxidising agents is a non-poisonous compound known as *pseudomorphine*, which is also present in opium. Its structure is still unknown.



The action of dehydrating agents is either to produce condensation of two or more molecules and form tri- and tetra-morphine or, if hydrochloric acid is used, to eliminate water with the production of a substance known as *apomorphine*, $C_{17}H_{17}NO_3$, in which two phenolic hydroxyls are present.

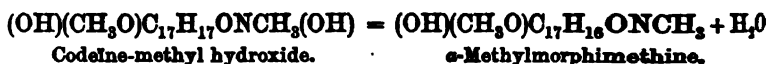
Our knowledge of the structure of morphine and codeine from this point centres round the recent investigations of Vongerichten,¹ of Knorr and of Pschorr.²

By the distillation of morphine over zinc dust, Vongerichten and Schrötter obtained *phenanthrene* together with a series of bases—ammonia, trimethylamine, pyrrole, pyridine, and a substance, morphidine, since recognized as a mixture of two bases. The appearance of phenanthrene is sufficiently interesting, but in consequence of the high temperature used in the reaction, no proof is afforded of its

¹ See various papers in the *Berichte* from 1896 onwards.

² See various papers in the *Berichte*, 1889, 1894, 1897, 1898, 1899, 1903, and *Annalen*, 1898, 301, 1; 1899, 307, 171.

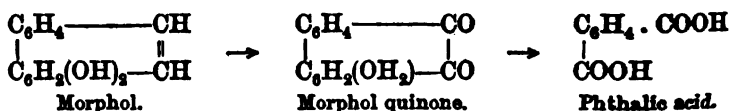
existence in the alkaloid itself. Further confirmation was necessary. Vongerichten and Schrötter then submitted codeine to the process of exhaustive methylation. On distilling codeine-methyl hydroxide a new base is formed, to which the name *α-methylmorphimethine* has been given.



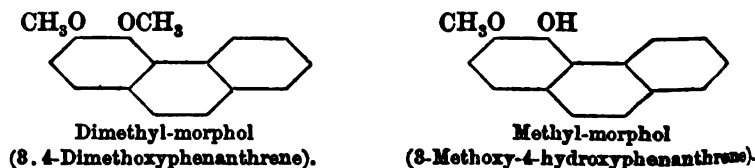
This new compound still contains hydroxyl, and when heated with hydrochloric acid or acetic anhydride is resolved into methyldihydroxyphenanthrene and dimethylamino-ethanol.



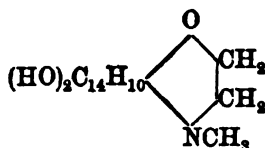
The structure of methyldihydroxyphenanthrene was determined by its resolution into dihydroxyphenanthrene or *morphol* and into phenanthrene, and since morphol is converted successively by oxidation into the corresponding quinone and into phthalic acid, both hydroxyls must be present in the same ring.



The structure of dimethyl- and monomethyl-morphol has since been confirmed by Pschorr and Sumuleanu and by Pschorr and Vogtherr,¹ who obtained them synthetically.



By combining the results of the various reactions carried out in the manner described, Knorr originally suggested a formula for morphine in which the methylamino-ethanol group was attached to the phenanthrene nucleus as an oxazine or *morpholine* group thus:

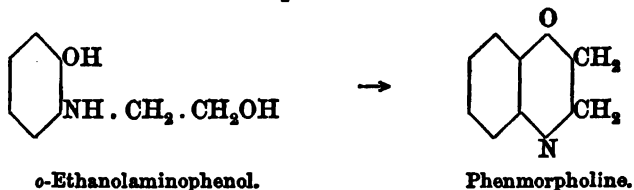


¹ Ber., 1900, 33, 1810; 1902, 35, 4412.

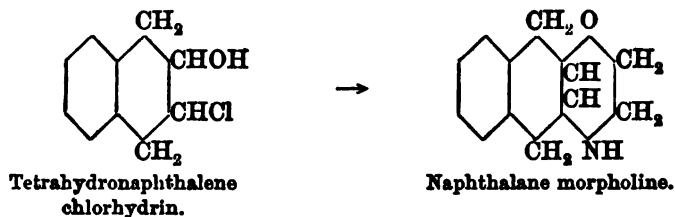
but this view is now abandoned, and the ethanol group is at present regarded by Knorr¹ as a secondary product derived from an original vinyl group.

The reasons for this are based upon the different behaviour of the artificial morpholine derivatives.

A variety of these compounds have been prepared synthetically by Knorr. Such, for example, is *phenmorpholine*, obtained by internal condensation of *o*-ethanolaminophenol.



Another interesting synthetic product is the base *naphthalane morpholine*,² which is obtained by condensing tetrahydronaphthalene chlorhydrin with ethanolamine.



Although the *N*-methyl derivative of this compound closely resembles morphine, both in its physiological action and in the character of its disintegration products, yet the dimethylamino-ethanol derivatives of dihydronaphthalene differ greatly in stability from methylmorphimethine, and they cannot therefore be similarly constituted. The same view has been arrived at on other grounds by Freund³ from the study of the closely related alkaloid, thebaine.

This connection between codeine, morphine, and thebaine has been arrived at in the following way: *codeinone*, which is obtained by the oxidation of codeine, is a ketone and yields, when heated with dilute hydrochloric acid, *thebenine*, and with strong hydrochloric acid, *morphothebaine*. Now, as both these compounds are obtained in the same manner from thebaine, the two alkaloids must be nearly related.⁴ Moreover, codeinone is decomposed by acetic anhydride into methylamino-ethanol and 8-methoxy-4,6-dihydroxyphenanthrene,

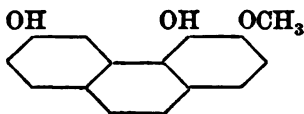
¹ *Ber.*, 1905, 38, 8148.

² *Ber.*, 1905, 38, 8284.

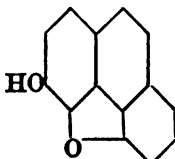
³ *Annalen*, 1899, 307, 171.

⁴ *Ach and Knorr, Ber.*, 1908, 38, 8067.

which is related to *thebaol* (p. 603). Thus, codeine is a derivative of 8.4.6-trihydroxyphenanthrene.

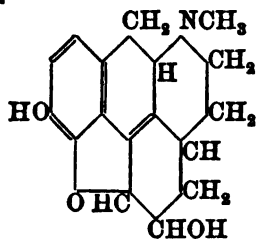


Pschorr¹ regards the nitrogen atom in the three alkaloids as forming part of a pyridine ring and bases his view on the persistence of the 'indifferent' oxygen atom when the nitrogen complex is entirely detached. Thus, Vongerichten obtained from the stereoisomeric or β -methylmorphimethine *morphenol*, which probably has the formula:

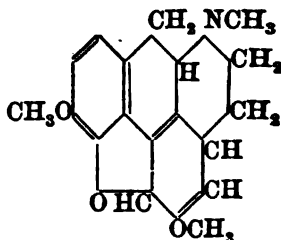


Morphenol.

and Pschorr formulates the structure of morphine and thebaine as follows:



Morphine.



Thebaine.

Thebaine was discovered in opium by Thiboumery in 1835. It was investigated by Pelletier, and its composition ($C_{19}H_{21}NO_3$) was correctly determined by Anderson. Our knowledge of its structure, as far as it is known, is mainly the result of the careful and systematic study which Martin Freund² has devoted to the subject since 1894.

The molecular formula of the three alkaloids, morphine, codeine, and thebaine, would in itself suggest a connection between them.



¹ The present position of the morphine problem is discussed by Pschorr and Einbeck, *Ber.*, 1907, 40, 1980, and by Knorr and Hörlein, *Ber.*, 1907, 40, 2042.

² *Ber.*, 1896, 28, 941; 1897, 30, 1857; 1899, 32, 168.

Such a relationship has already been shown to exist. Thebaïne is a tertiary base; it contains two hydrogen atoms less than morphine, no hydroxyl, but two methoxyl groups. As, in addition, it yields tetramethylethylene diamine,



on exhaustive methylation, it contains a *N*-methyl group, and accordingly its formula may be written:

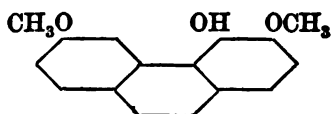


Thebaïne undergoes a similar decomposition to the other two alkaloids; for on boiling with acetic anhydride it is resolved into the acetyl derivatives of the nitrogen-free *thebaol* and of *methylamino-ethanol*, the latter furnishing a further proof of the presence of the methylamine radical.



Thebaïne methyl iodide in presence of silver acetate undergoes a similar change, but in this case, in addition to thebaol acetate the acetyl derivative of dimethylamino-ethanol is formed.

Thebaol was shown by Freund, using similar methods to those already described, to be a dimethoxy-hydroxyphenanthrene. It yields a quinone on oxidation resembling phenanthraquinone and possessing the properties of an ortho diketone, and on further oxidation passes into *o*-methoxyphthalic acid. The synthesis of thebaol-quinone by Pschorr and Seydel¹ from 2-nitro-isovanillin has definitely established the structure of thebaol as 4-hydroxy-3:6-dimethoxyphenanthrene.



It is clear from the foregoing that the constitution of thebaïne is intimately related to that of morphine and codeïne, and that the same key which would serve to unlock one structure would fit the other two. At present, however, the key is missing, and the structural formulæ which have been assigned must be regarded as provisional.

¹ Ber., 1902, 35, 4400.

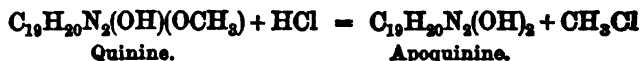
THE QUINOLINE ALKALOIDS

Quinine and Cinchonine. Among the various alkaloids which are found in cinchona bark, quinine and cinchonine are the most plentiful, the most important and the most carefully investigated. As it has been also shown that they are similarly constituted, there are certain advantages in discussing them together.

Both alkaloids were discovered in 1820 by Pelletier and Caventou, and the molecular formulae of the anhydrous bases were found to be:

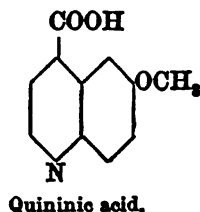
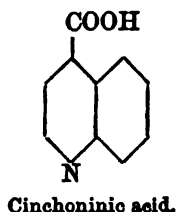


Both alkaloids are bi-tertiary bases, that is to say, the two nitrogen atoms are present as tertiary groups. Of the two oxygen atoms of quinine one is present as hydroxyl, the other as methoxyl. By heating quinine with strong hydrochloric acid the methyl group is eliminated as methyl chloride and the product is known as apo-quinine.

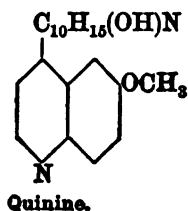
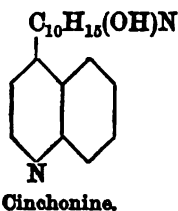


The oxygen atom of cinchonine represents a hydroxyl group.

Oxidation of Quinine and Cinchonine. The products obtained by oxidising the two alkaloids has shown that each alkaloid is sharply divisible into two parts. With energetic oxidising agents cinchonine yields cinchoninic acid, whilst quinine yields quininic acid. The structure of both acids is known and represented by the following formulae:



It will be seen that the two acids stand in the same relation as the alkaloids from which they are derived, and thus 'the second-half', as it is termed, is probably identical in both.

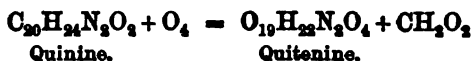


The further investigation of their structure, which up to this point was clearly explained by Skraup, has offered unexpected difficulties, and the constitution of 'the second-half' is not yet finally and definitely established.

Among the mass of materials which have accumulated on the subject, those only have been selected which appear to have a direct bearing on the problem under discussion. If cinchonine is oxidised with permanganate, formic acid is split off and a new base *cinchotenine* is formed.



Similarly quinine yields *quitenine*.



Cinchotenine still contains the original hydroxyl group of cinchonine, and in addition a carboxyl group, since it yields an ester; but whilst cinchonine forms an additive compound with hydrogen iodide, cinchotenine has lost this power. Thus, in all probability, the change depends on the oxidation of an unsaturated side-chain.



The same kind of difference is exhibited between quinine and quitenine.

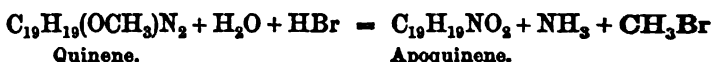
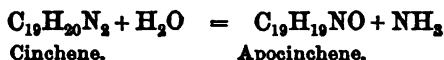
Koenigs¹ found that when cinchonine is acted upon with a mixture of phosphorus pentachloride and oxychloride the hydroxyl group is replaced by chlorine and forms *cinchonine chloride*. Alcoholic potash removes a molecule of hydrogen chloride, and a new oxygen-free base is formed, which was named by Koenigs *cinchene*.



¹ Various papers in the *Berichte*, beginning with *Ber.*, 1880, 13, 286, to the present time.

Quinine behaves similarly and yields *quinene*, $C_{19}H_{19}(OCH_3)N_2$. To these two substances, cinchene and quinene, Koenigs and his collaborators¹ have devoted their attention with the object of establishing the structure of the 'second-half' of the molecule.

On prolonged boiling with strong hydrobromic acid, ammonia is split off and water taken up by both compounds, yielding *apocinchene* in one case and *apoquinene* in the other.

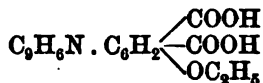


If, on the other hand, cinchene and quinene are heated with 25 per cent. phosphoric acid solution under pressure, two molecules of water are taken up, and lepidine and *p*-methoxy-lepidine are respectively formed, together with a second product which is common to both and is named *meroquinene*. The structure of meroquinene has a special significance, as it may be taken to represent the second-half of the two alkaloids.



Structure of Apocinchene. Koenigs succeeded by oxidising the ethyl derivative of apocinchene in resolving it step by step into three new products, which have been identified as derivatives of quinolylphenol.

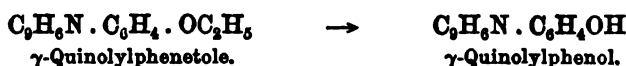
The first is known as *ethylapocinchenic acid*, the second as the lactone of *hydroxyethylapocinchenic acid*, and the third has been identified as *quinolylphenetole dicarboxylic acid*.



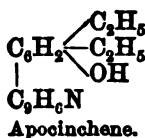
Again, if ethyl apocinchenic acid is boiled with hydrobromic acid, carbon dioxide and ethyl bromide are removed and *homapocinchene* is formed. The ethyl derivative of the latter yields on oxidation ethylhomapocinchenic acid; and if the silver salt is heated, γ -quinolylphenetole results. Finally, γ -quinolylphenetole is converted into γ -quinolylphenol with hydrobromic acid.

¹ *Annalen*, 1906, 347, 143.

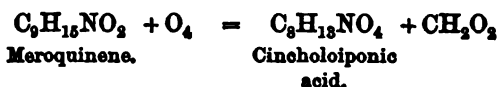
The series of changes are represented as follows :



Putting the above facts together, the probable formula for apocinchene is that of a quinolyl diethylphenol.

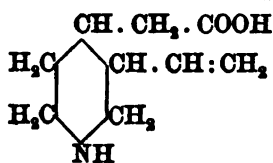


Structure of Meroquinene. In addition to the method already described for the preparation of meroquinene, Koenigs succeeded in obtaining it by the direct oxidation of cinchonine with chromic acid. By further oxidation with cold permanganate in presence of sulphuric acid meroquinene is converted into *cincholoiponic acid*, $\text{C}_8\text{H}_{13}\text{NO}_4$.

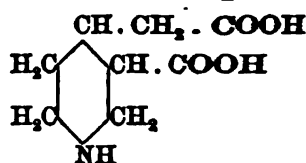


From the latter Skraup obtained by careful oxidation with permanganate small quantities of a second acid which he termed *loiponic acid*, $\text{C}_7\text{H}_{11}\text{NO}_4$. All these compounds appear to contain a piperidine nucleus, the presence of which has been demonstrated in various ways. Thus, when meroquinene is heated with hydrochloric acid to 240° with or without the addition of mercuric chloride γ -methyl- β -ethylpyridine is formed, whilst strong sulphuric acid converts cincholoiponic acid into γ -methylpyridine; finally, Koenigs showed that loiponic acid is transformed by heating with potash into an isomeric acid which is identical with synthetical hexahydro-cinchomeronic acid (piperidine- β - γ -dicarboxylic acid). The other reactions for meroquinene indicate that it is a secondary base, with an unsaturated side-chain (it forms an additive compound with bromine) and a carboxyl group (it forms an ester with alcohol).

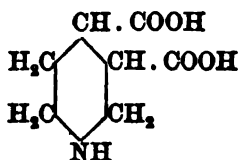
These facts taken together point to the following as the most probable formulae for meroquinene and its oxidation products,



Meroquinene.

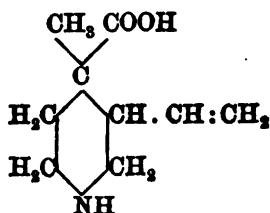


Cincholoiponic acid.

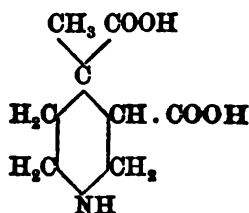


Loiponic acid.

or, less probably,



Meroquinene.



Cincholoiponic acid.

It therefore follows that the 'second-half' is a piperidine nucleus, and, moreover, that it is attached to the γ -carbon of the quinoline nucleus by the carbon atoms of the γ -side-chain, since on oxidation meroquinene and cinchoninic acid are produced, each of which has a carboxyl in the γ -position. By the same process the hydroxyl group disappears, and must also form part of the γ -side-chain.

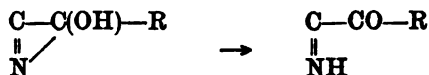
It will be seen from this summary that the structure of the 'second-half' and also the nature of the union between the piperidine and the quinoline nucleus is still uncertain, in addition to which the position of the hydroxyl group in the γ -side-chain is undetermined and the exact function of the γ -side-chain unknown. A certain amount of light has been thrown on these obscure points by the study of a substance known as *cinchotoxine*.

Structure of Cinchotoxine. The monoalkyl iodides of cinchonine produced by the direct action of the alkyl iodide, and in which the alkyl iodide has been shown to attach itself to the tertiary nitrogen

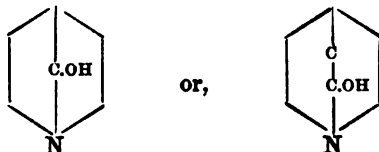
of the 'second half', lose hydrogen iodide when decomposed by alkalis and form alkyl cinchonines. The methyl derivative,



obtained in this way was found by Miller and Rohde¹ to combine with phenylhydrazine and yield a hydrazone, whilst cinchonine itself does not give this reaction. If, however, cinchonine is submitted to the prolonged action of phenylhydrazine dissolved in dilute acetic acid at a temperature of 100°, combination ensues. The molecular rearrangement which evidently takes place was subsequently found to occur without the addition of phenylhydrazine by merely heating with acetic acid. The new compound is a base, isomeric with cinchonine, but possessing highly poisonous properties, on account of which it was named *cinchotoxine*. Quinine behaves in precisely the same manner and gives rise to *quinotoxine*. Cinchotoxine is a ketone and not an aldehyde since it forms a hydrazone and oxime, but does not reduce silver oxide. It is also a secondary base. How is the change from alcohol to ketone and from tertiary to secondary base to be explained? The change is probably tautomeric of the imidol-amide type (p. 180)



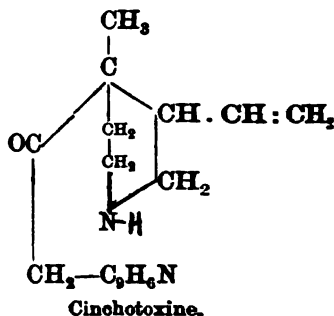
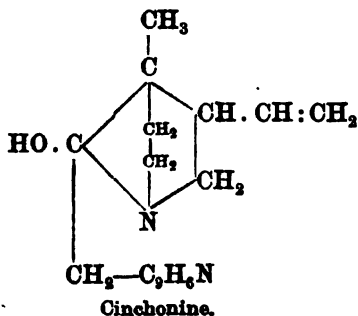
It would therefore appear that the link which binds the hydroxyl-carbon to the nitrogen of the piperidine nucleus is dissolved, and that the hydroxyl consequently occupies the α -position. But this is not all. The hydroxyl group has also been shown to be attached to the γ -carbon since it disappears in meroquinene, and must therefore form part of the γ -side-chain. To represent the hydroxyl as occupying simultaneously an α - and γ -position necessitates a bridged ring of the following character:—



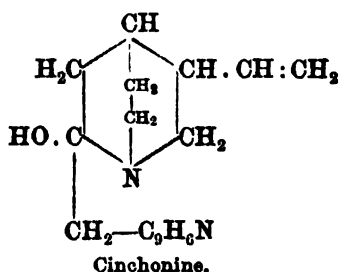
The formation of a ketone from cinchonine also means that the hydroxyl-carbon is already linked to a second carbon atom. This second carbon probably serves as the bond which unites the two halves of the molecule. Such at least is the interpretation which

¹ Ber., 1894, 27, 1187, 1279; 1895, 28, 1056.

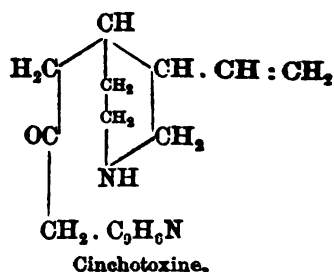
has been placed upon these facts, and finds expression in the following alternative formulae for cinchonine and cinchotoxine:—



or,



or,



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